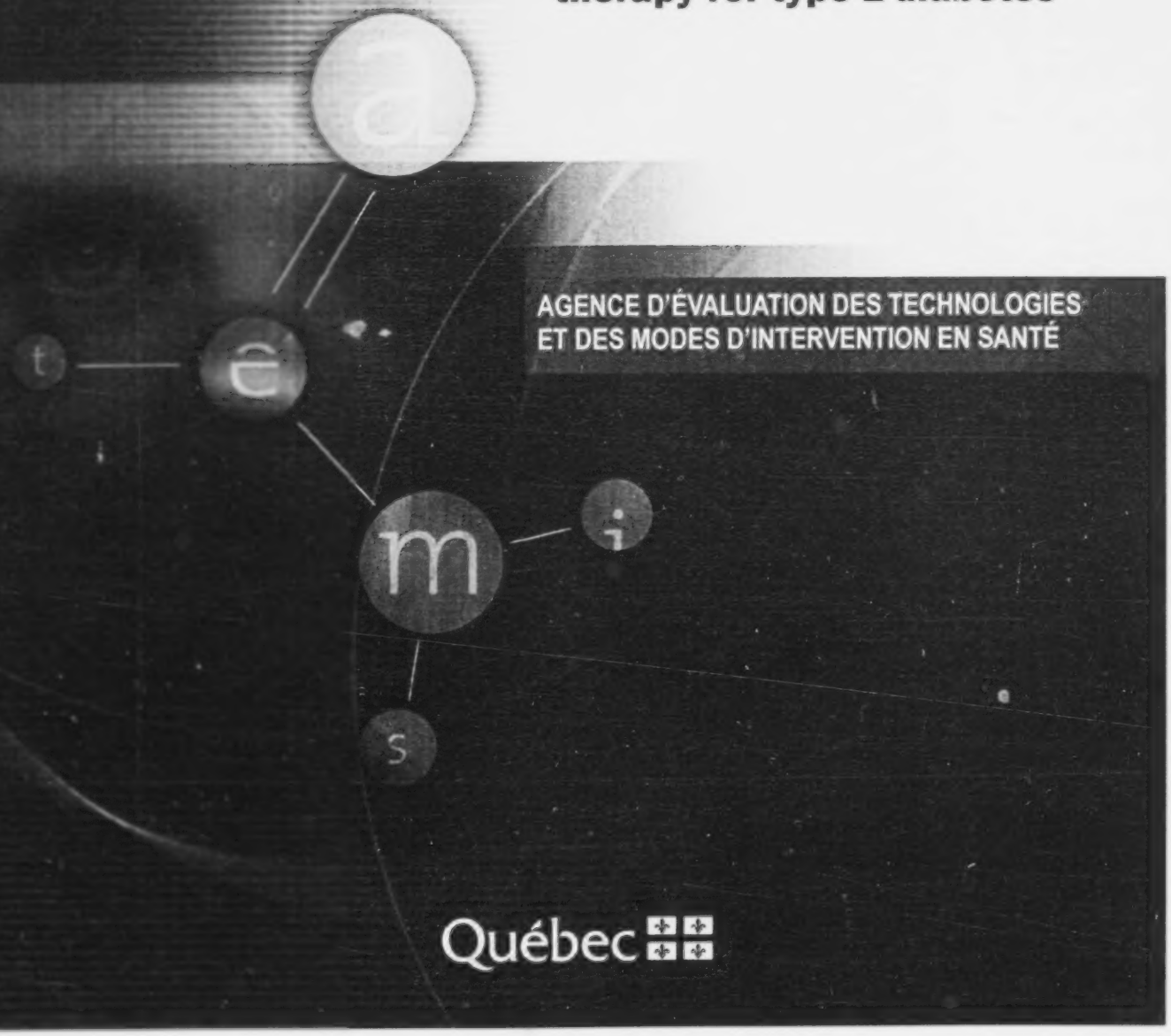
Comparison of the insulin pump and multiple daily insulin injections in intensive therapy for type 1 diabetes



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Comparison of the insulin pump and multiple daily insulin injections in intensive therapy for type 1 diabetes

Report prepared for AETMIS
by Brigitte Côté and Carole St-Hilaire

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Agence d'évaluation des technologies et des modes d'intervention en santé
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FOREWORD

Diabetes is a chronic, incurable disease, and its prevalence in the Québec population is on the rise. Approximately 30,000 Quebecers have type 1 diabetes, and the only treatment currently available is insulin therapy. Treatment with insulin injections can be conventional (two injections per day) or intensive (four to seven injections per day), but in both cases, the goal is normoglycemia. Glycemic control is essential, both for preventing short-term problems, such as hypoglycemic and ketoacidotic episodes, and for preventing long-term complications, such as diabetic retinopathy, nephropathy and neuropathy.

For several years now, continuous subcutaneous insulin infusion, or the insulin pump, has been an alternative to multiple daily insulin injections in intensive therapy for type 1 diabetes. Pump therapy, which is not covered by the public plan in Québec, avoids repeated injections and offers greater flexibility in adjusting the insulin dose on the basis of the level of physical activity and food intake.

In this context, the *Ministère de la Santé et des Services sociaux* asked the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) to assess insulin pump therapy. This report examines the safety and efficacy of this technology and the economic aspects of introducing it into Québec's health-care system, and presents the patient and health professional perspectives in the Québec context.

An evaluation of the evidence indicates that this technology is safe for motivated patients who are adequately trained and supported by a specialized team and that the improvement in glycemic control offered by the pump, though very modest for the general population of diabetic patients, could be significant for a specific subgroup of patients. Although the cost-effectiveness data for the insulin pump are limited, they do seem to indicate that its use is efficient when it is prescribed to selected patients.

In light of this analysis, AETMIS recommends, among others: 1) that a clear, consistent policy be developed for the use of the insulin pump as a treatment modality for a limited, selected group of patients with type 1 diabetes, with specific prescription and coverage modalities; and 2) that a multidisciplinary task force be formed and specifically charged with defining insulin pump use (patient selection, prescription and follow-up criteria and tools) and the procedures for implementing an insulin pump access program (designated centres, care teams, evaluation) in the current Québec context.

In submitting this report, AETMIS wishes to contribute to the optimal use of the insulin pump in intensive type 1 diabetes therapy for the greater benefit of all patients with this disease.

Luc Deschênes
President and Chief Executive Officer

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This report was prepared at the request of the *Agence d'évaluation des technologies et des modes d'intervention en santé* (AETMIS) by **Brigitte Côté**, MD, MSc (Public Health), medical specialist in public health and consulting researcher, and **Carole St-Hilaire**, PhD (Public Health), economist and consulting researcher.

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CONFLICT OF INTERESTS

None declared.

SUMMARY

INTRODUCTION

This report examines the safety, efficacy and cost-effectiveness of the insulin pump compared to multiple daily insulin injections for the treatment of type 1 diabetes, a chronic, incurable disease whose onset generally occurs at an early age. Insulin therapy and its modalities have evolved in the past few years, and the intensive therapy recommended in all the practice guidelines can be administered by continuous subcutaneous insulin infusion (pump) or by multiple daily insulin injections. Clinical studies identify two types of basal insulin used in multiple daily injections: NPH[1] and glargine[2].

DESCRIPTION OF THE TECHNOLOGY

Insulin pump therapy is technically referred to as continuous subcutaneous insulin infusion. It is a method of administering short-acting insulin subcutaneously by means of a portable, battery-operated, programmable infusion pump with a tube and a Teflon or metal cannula specially designed for this purpose.

SEARCH METHOD

The literature search identified two health technology assessment agency (HTA) reports, one published in August 2002 by an HTA agency in Great Britain, the other in 2000 by the Catalonian HTA agency. To complement this information, we examined the literature published since 2002. The perspective of patients who use the pump and of health professionals who have experience with it was also explored by means of a self-administered questionnaire (patients) and face-to-face interviews (health professionals).

RESULTS

Indicators

Safety is evaluated in terms of mortality and severe hypoglycemic episodes and ketoacidotic episodes due to pump malfunction. The standard indicator of quality of glycemic control is glycosylated hemoglobin (HbA_{1c}). The HbA_{1c} level is an indicator of glycemic control over the past two to three months. The higher this level, the higher the frequency of complications. The HbA_{1c} concentration and the mean blood glucose level are widely used in clinical and research settings as surrogate outcomes for predicting long-term complications. These two indicators are the ones used in this report to assess therapeutic efficacy. The Diabetes Quality of Life (DQOL) questionnaire, which measures the impact of diabetes on four areas of daily life, and the version adapted for youth, the DQOLY (Diabetes Quality of Life for Youth), were used as quality-of-life instruments.

Safety

Randomized, controlled trials have found no difference, in children or adults, in the incidence of severe hypoglycemic episodes with the pump compared to multiple injections. Nonrandomized studies have reported fewer severe hypoglycemic episodes in pump-treated patients, but this can be explained by the choice of subjects in such studies, where pump therapy is offered to those patients who are most likely to benefit from it. Two nonrandomized studies, one involving adults selected at the beginning of the study, the other involving children, found that pump therapy and multiple injections with glargine are more effective than multiple injections with NPH in reducing the incidence of

1. Neutral protamine Hagedorn (NPH) is a slow-acting insulin.
2. A novel slow-acting insulin that has been approved but which is not yet available in Canada.

severe hypoglycemic episodes. As for the incidence of ketoacidotic episodes, studies have found no significant difference between pump therapy and multiple injections, although the absolute number of ketoacidotic episodes is higher with the pump.

Efficacy

Comparison of pump therapy and multiple injections with NPH

As regards efficacy, data from randomized, controlled trials indicate that for the general population of adult diabetic, the pump can lead to a modest improvement in glycemic control (mean decrease of 0.51 to 0.6% in the HBA_{1c} level) compared to multiple injections with NPH, with no additional risks. For the general population of diabetic children, randomized, controlled trials have not found the pump to have any advantage over multiple injections with NPH. In patients selected because of inadequate glycemic control (HBA_{1c} level $\geq$ 8.5%), one randomized, controlled trial noted a greater improvement with the pump in the adults (0.84% decrease in the HBA_{1c} level). Nonrandomized studies involving children selected according to various criteria report a greater improvement with the pump as well, although it cannot be quantified.

Comparison of pump therapy and multiple injections with glargine

In terms of glycemic control, the pump is as effective as multiple injections with glargine in adults. However, for some patients who fail to achieve glycemic control with multiple injections with glargine, the pump could be an option. The effect of insulin glargine on glycemic control is difficult to evaluate in children, but this new treatment modality does not seem to confer the same benefits as it does for adults, except that it reduces the incidence of severe hypoglycemic episodes.

Quality of life

The data on the impact of the pump on quality of life from randomized or cohort studies involving the general population of type 1 diabetics do not indicate any improvement. In adult patients selected because of inadequate glycemic control, two studies report that the pump led to a significant improvement in various aspects of quality of life. Randomized, controlled trials report no significant effect on the quality of life of children who use the pump. Only one such trial found a tendency in favour of pump therapy with regard to certain domains covered by the DQOLY questionnaire, particularly satisfaction with the treatment.

PERSPECTIVE OF PATIENTS WHO USE THE PUMP

In all, 34 people, including 30 pump users, voluntarily responded to a survey conducted in Québec. Since the sample was small, the respondents' comments cannot be generalized to all type 1 diabetics who are using or previously used the pump. It emerges from all the responses that diabetics who presently use the pump derive from it benefits they consider important with regard to several aspects of their daily life. A number of characteristics differentiated the pump users who participated in our survey from most other type 1 diabetics. They were more motivated than average, and some of them were highly organized. They were using the pump successfully and were generally enthusiastic about the technology. These patients had come to use the pump after experiencing considerable difficulty controlling their diabetes (severity bias). They were therefore more likely to benefit from the pump than the typical diabetic patient.

PERSPECTIVE OF HEALTH PROFESSIONALS

All the health professionals consulted agree that the current pumps are safe, if the patient is conscientious, serious, motivated and disciplined, and has received complete training. In Québec, a number of them prescribe the insulin pump and train their patients, both adults and children. For adults, opinions are divided as to the comparative effectiveness of the pump in terms of glycemic control. All of the professionals in question say that the pump is effective in a minority of carefully selected patients. For children, clinical opinions are more categorically in favour of the pump. All the clinicians interviewed conclude that the pump is not for everyone, but only for selected candidates.

ECONOMIC ASPECTS

The only thorough study published to date indicates that pump therapy is a cost-effective investment, if prescribed to patients who are most likely to benefit from it, namely, those who experience more than two severe hypoglycemic episodes per year and who have to be hospitalized at least once a year for hypoglycemia. Two other economic studies were published recently, but only as abstracts, with the result that the methodological quality and assumptions underlying the modelling cannot be assessed. A paper presented at a recent conference maintains that pump therapy is more effective in the long term than multiple injections, but at a much higher cost. The present Québec-based cost analysis includes the cost of the pump, accessories, patient training and supplies. Compared to multiple insulin injection therapy, the equivalent annual cost differential of pump therapy is estimated at CA$4,756 per user. This estimate takes into account the fact that a pump is replaced every five years and that, at that point, training is required, which is a major disbursement. It should be noted that the total anticipated cost for each diabetic who uses an insulin pump will be proportional to the mean life expectancy of the diabetics thus treated.

CONCLUSION

According to the scientific literature, the insulin pump is effective and does not involve greater risks than the comparator therapy, multiple injections with NPH, if precautions are taken. However, the efficacy gain is clearly more pronounced for patients—both adults and children—who meet specific clinical and psychosocial criteria. Study data indicate that the pump's efficacy is comparable to that of multiple injections with glargine for all adult diabetic patients. Since the pump is very expensive, and since insulin glargine should soon be available in Québec, there is less interest in pump therapy for adult diabetics. Nonetheless, for some adult patients who may not be able to achieve adequate glycemic control via multiple injections with glargine, the pump could prove to be a cost-effective option. For children, glargine seems to be less promising than for adults.

RECOMMENDATIONS

AETMIS recommends that:

1) as set out in the Canadian practice guidelines, the preferred therapeutic approach to type 1 diabetes, in both adults and children, be based on intensive therapy with multiple daily insulin injections;

2) therapy by continuous subcutaneous insulin infusion (insulin pump) be recognized in Québec as a treatment modality that might be indicated for a limited, selected group of type 1 diabetics (various selection criteria based on expert opinions are cited in this report);

3) the *Ministère* consider setting up a multidisciplinary task force (including *Diabète Québec*, and the clinical and research communities) charged with:

- identifying consensus criteria for patient selection and for prescribing and monitoring insulin pump therapy;
- designating clinics that would participate in the implementation of pump therapy and determining the composition and role of the professional team required;
- developing common candidate selection, patient education and follow-up tools;
- monitoring the implementation of pump therapy; and
- reevaluating the use of pump therapy in Québec some time after it is introduced;

4) the consensual criteria for the use of the pump be reviewed periodically in light of the new evidence that becomes available after this report, in particular, from studies comparing the insulin pump and multiple injection therapy with glargine, since glargine may soon be available in Canada (technology watch);

5) a clear, consistent policy governing the use of the insulin pump be developed and made part of a broader initiative for managing diabetes in Québec that would take into account the need to increase the ability of Québec's health-care system to offer intensive therapy to all type 1 diabetics;

6) two options for standardizing the prescription and coverage modalities be examined:

- consider the pump an exceptional treatment modality for exceptional patients, with access granted by the *Régie de l'assurance maladie du Québec* (RAMQ) on a case-by-case basis according to the criteria established by the above-mentioned task force and/or on request by a physician;
- institute systematic pump prescription and utilization auditing and monitoring procedures based on set criteria in collaboration with the clinical settings concerned, possibly by creating a registry of pump-treated patients or developing tools for selecting cases on a priority basis within a predetermined budget allowance;

7) a full range of technical services be provided in French in Québec by the manufacturers and distributors of insulin pumps; and

8) research on patient selection criteria and the cost-effectiveness of insulin pumps in the Québec context be considered an important avenue of investigation by the *Fonds de la recherche en santé du Québec* (FRSQ).

LIST OF ABBREVIATIONS

AATRM	*Agència d'Avaluació de Tecnologia i Recerca Mèdiques*
ADDQoL	Audit of Diabetes-Dependent Quality of Life
AETS	*Agencia de Evaluación de Tecnologías Sanitarias*
AUC	Area under the curve
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CDA	Canadian Diabetes Association
CI	Confidence interval
CPI	Consumer price index
DCCT	Diabetes Control and Complications Trial
DQOL	Diabetes Quality of Life
DQOLY	Diabetes Quality of Life for Youth
DSQOLS	Diabetes-Specific Quality of Life Scale
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EACD	Equivalent annual cost differential
ECRI	Emergency Care Research Institute
EDIC	Epidemiology of Diabetes Interventions and Complications
FDA	Food and Drug Administration
FRSQ	*Fonds de la recherche en santé du Québec*
GP	Glycosylation gap
HbA_{1c}	Glycosylated hemoglobin
HGI	Hemoglobin glycosylation index
HPFB	Health Products and Food Branch (Health Canada)
INAHTA	International Network of Agencies for Health Technology Assessment
INPUT	INsulin PUmp Therapy (British advocacy group that promotes the use of the pump)
INSPQ	*Institut national de santé publique du Québec*
MAGE	Mean Amplitude of Glycemic Excursion
MAUDE	Manufacturer and User Facility Device Experience (FDA database)
MBG	Mean blood glucose
MDI	Multiple daily injections
MHRA	Medicines and Healthcare Products Regulatory Agency
NA	Data not available
NHS	National Health System

NICE	National Institute for Clinical Excellence
NPH	Neutral protamine Hagedorn (a basal insulin)
NS	Difference not significant
OR	Odds ratio
PMPRB	Patented Medicine Prices Review Board
PUMP	Pump Management for Professionals (group of professionals in Great Britain)
QALY	Quality-adjusted life-year
RAMQ	*Régie de l'assurance maladie du Québec*
RCT	Randomized, controlled trial
RR	Relative risk
SBGM	Self Blood Glucose Measurement
SF-36	Medical Outcome Study 36-item Short-Form Survey
UKPDS	UK Prospective Diabetes Survey
WESDR	Wisconsin Epidemiological Study of Diabetic Retinopathy

GLOSSARY

Albuminuria: The presence of albumin in the urine, often because of increased renal tubule patency. It is a clinical sign of diabetic nephropathy.

Blood glucose level: The normal blood glucose level is < 6.1 mmol/L. Hyperglycemia is a blood glucose level above this figure.

Carotid intima: The innermost layer of the carotid artery.

Conventional therapy: Two daily injections of a mixture of slow-acting and short-acting insulins.

Creatinine clearance: A renal function test for determining the glomerular filtration rate and that serves as a means of assessing the severity of nephropathy. It measures the ratio of the urinary creatinine output per minute to the plasma creatinine concentration. It expresses, in millilitres per minute, the volume of plasma from which the kidneys are capable of completely eliminating the creatinine in one minute.

Diabetic coma: A coma complicating decompensated diabetes with ketoacidosis.

Diabetic nephropathy: A condition of the kidneys caused by hardening of the blood vessels, which impairs the kidney's ability to filter proteins. This can lead to renal failure. It progresses from a subclinical stage to the microalbuminuria stage (clinically detectable) to proteinuria and, finally, to renal failure.

Diabetic neuropathy: Injury to the peripheral nervous system characterized by tingling and prickling sensations or a loss of sensation. It can cause pain or paralysis.

Diabetic retinopathy: A condition of the blood vessels that supply the retina. It causes lesions ranging from initial asymptomatic alterations observed during an ophthalmoscopic examination to severe processes leading to blindness.

Dialysis: A treatment for renal failure consisting in separating solutes in a solution by diffusion across a semipermeable membrane.

Hyperglycemia: An elevated blood glucose level. It is considered pathologic starting at 6.1 mmol/L. A blood glucose level ≥ 7.0 mmol/L is diagnostic of diabetes.

Hyperinsulinemia: An excess amount of insulin in the blood. When pronounced, it results clinically in the hypoglycemic syndrome.

Hypoglycemia: A low blood glucose level (upper limit of 4.0 mmol/L for patients on insulin), with the appearance of different symptoms, depending on the severity of the hypoglycemia. They range from tremor, palpitations and sweating to dizziness, mental confusion and a loss of consciousness. The symptoms are relieved after the administration of carbohydrates.

Insulin glargine: A novel slow-acting insulin that was recently approved but which is not yet commercially available in Canada. It has a prolonged absorption profile over close to 24 hours with no peak action.

Intensive therapy: Multiple daily injections of slow- and short-acting insulins or a continuous subcutaneous insulin infusion.

Ketoacidosis: The result of a grossly deficient regulation of carbohydrate and lipid metabolism that leads to an accumulation of ketone bodies. It is usually triggered by an interruption in the insulin supply or by an acute infection, trauma or an infarction that makes usual treatment with insulin unsuitable. Its symptoms are polyuria, nausea and vomiting followed by drowsiness and lethargy. If not treated properly, ketoacidosis evolves toward diabetic coma.

Macroangiopathy: A disease of the large and medium-size arteries; atherosclerosis.

Macrovascular complications: See **macroangiopathy**.

Microalbuminuria: A subtle but pathological increase in urinary albumin excretion (30 to 300 mg/day). In diabetics, it is indicative of incipient nephropathy.

Microangiopathy: A disease of small vessels—arterioles, capillaries and venules—characterized by basal membrane thickening. In diabetics, it causes serious cutaneous and especially retinal and renal complications. Some even consider it almost specific to diabetes mellitus, especially when the latter is prolonged and poorly controlled.

Microvascular complications: See **microangiopathy**.

Normoglycemia: A normal blood glucose level.

NPH (neutral protamine Hagedorn) insulin: The most frequently used slow-acting insulin. It has a mean duration of action of 14 ± 3 hours, with a peak between three and five hours after injection.

Photocoagulation: A procedure in which a laser is used to coagulate tissue.

Proteinuria: The presence of protein in the urine, a sign of diabetic nephropathy.

Renal failure: A syndrome defined as a decrease in the kidney's glomerular filtration rate. It is also characterized by hydroelectrolytic and endocrine abnormalities. Renal failure is the end stage of diabetic nephropathy.

Serum creatinine level: The normal serum creatinine level is 6 to 15 mg/L (60 to 130 µmol/L). The creatinine level is an indicator of renal function.

Severe hypoglycemia: Hypoglycemia that can lead to mental confusion, a coma or seizures. The individual requires assistance and may loose consciousness. The blood glucose level is usually less than 2.8 mmol/L. Severe hypoglycemia often occurs during sleep or when the individual does not notice any neurovegetative symptoms and can therefore not take the necessary steps to correct his/her blood glucose level.

Vitiligo: A skin pigmentation disorder characterized by well-defined depigmented patches surrounded by a darker area, with no pathological changes. Its cause is unknown. The patches, which can occur on various areas of the body, are often symmetrical and are generally refractory to treatment.

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1 INTRODUCTION

Diabetes is a metabolic disorder characterized by hyperglycemia due to impaired insulin secretion and/or impaired insulin action. It is associated with serious long-term sequelae affecting various organs [Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003]. Its prevalence in the population is on the rise. There are three main types of diabetes, based on their cause [Harris and Lank, 2004]. Type 1 diabetes results from an immune or idiopathic process in which pancreatic beta-cells are destroyed, which usually leads to absolute insulin deficiency. It is estimated that 10% of diabetics have type 1 diabetes [Health Canada, 2002]. Type 2 diabetes is characterized by insulin resistance with relative insulin deficiency or by a secretion abnormality accompanied by insulin resistance. This type of diabetes is associated with obesity and physical inactivity. The third type, gestational diabetes, occurs during pregnancy but disappears after delivery in most cases. This report examines the treatment of type 1 diabetes only.

The goal of treating type 1 diabetes is to achieve normoglycemia. Glycemic targets vary according to the patient's age and the presence of various risk factors [Canadian Diabetes Association, 2003]. The subcutaneous administration of insulin is the basis of type 1 diabetes therapy. For the vast majority of patients, the recommended therapy has gone from a frequency of two injections per day of a mixture of insulins (conventional treatment before 1993) to intensive therapy involving several injections (four to seven) per day. New types of insulin and other modes of administration have been developed in an effort to improve glycemic control and the quality of life of diabetics. Since 1976, researchers have been working on developing a device, called the "insulin pump", that would make it possible to mimic normal pancreatic function (which varies insulin secretion according to basal needs, the level of physical activity and food intake) and to thus permit better dose adjustments while at the same time avoiding repeated injections.

In this context, the *Ministère de la Santé et des Services sociaux* (MSSS) requested that AETMIS evaluate insulin pumps and asked it the following questions:

- "Is the insulin pump safe, effective and cost-effective for treating type 1 diabetes in adults and children in comparison to intensive therapy with multiple insulin injections?
- "If so, in what conditions and for which patients?
- "Would it be worthwhile to develop a program to manage and assess the impact of the insulin pump?
- "Would it be possible to carry out an assessment and monitor the preliminary results?
- "What training and personnel are required for patient selection and follow-up?"

This assessment examines the available scientific literature on the subject, looks at the economic implications of insulin pump therapy, and explores the perspective of Québec patients and health professionals.

2 TYPE 1 DIABETES

According to data published by the *Institut national de santé publique du Québec*, approximately 28,000 adult Quebecers have type 1 diabetes [INSPQ, 2002]. It is estimated that 2,000 to 2,500 youths from 0 to 17 years of age have this type of diabetes[3]. According to the Canadian Diabetes Association's 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada [CDA, 2003], the diagnostic criteria for diabetes are a fasting blood glucose ≥ 7.0 mmol/L or a random blood glucose ≥ 11.1 mmol/L, plus diabetic symptoms, or a blood glucose ≥ 11.1 mmol/L two hours after ingesting 75 g of glucose.

2.1 LIVING WITH TYPE 1 DIABETES

The optimal management of type 1 diabetes is a complex process requiring that the patients understand their disease, measure their blood glucose levels on a regular basis and inject themselves with insulin doses based on their blood glucose level, food intake and level of physical activity. Since insulin requirements vary with the level of activity and energy intake, patients treated by injections must stick to a planned activity and meal program once insulin is administered. The type of short-acting insulin used with the pump and the variable and programmable infusion rate that it permits give patients greater flexibility in activity and meal planning. On the other hand, since the body does not have a large insulin reserve, patients must exercise greater vigilance to ensure glycemic control. They may experience severe and/or symptomatic hypoglycemia requiring immediate assistance. In children, the phenomenon of hypoglycemic episodes is especially worrisome, since it can have repercussions on their neurological development [CDA, 2003].

3. Louis Rochette, statistician, INSPQ, personal communication, 2004.

2.2 INDICATORS USED TO MONITOR GLYCEMIC CONTROL

Since the advent of insulin in the treatment of type 1 diabetes in 1922, survival in diabetics has been prolonged, thus leading to the risk of long-term complications. The hypothesis that hyperglycemia as such has a harmful effect on the various target organs was officially proven in 1993 by the Diabetes Control and Complications Trial [DCCT Research Group, 1993], and since then, the various biochemical theories have increased the biological plausibility of a causal link between hyperglycemia and the occurrence of microangiopathy [Setter et al., 2003; Sheetz and King, 2002].

Most studies describe the quality of glycemic control on the basis of a standard indicator: the glycosylated hemoglobin (HbA_{1c}) level[4]. The HbA_{1c} level is an indicator of glycemic control over the past two to three months [Golden et al., 2003] that is widely used in clinical and research settings (the higher the level, the higher the frequency of complications). Self blood glucose measurement (SBGM)[5] profiles have revolutionized the clinical management of diabetes. Studies mention two indicators from daily profiles: the mean blood glucose (MBG) level and the mean amplitude of glycemic excursion (MAGE), which indicate glycemic fluctuations within a given day. In the past few years, devices for continuous glucose measurement in interstitial fluid have led researchers to propose new indicators of daily glycemic fluctuations, such as the area under the curve (AUC) [Weintrob et al., 2004a]. Some debate persists as to the clinical impact of glycemic excursion on diabetic complications. Service and O'Brien [2001], by modelling the relationship between the magnitude of daytime gly-

4. HbA_{1c} is a modified hemoglobin A characterized by the addition of a glycosyl group. HbA_{1c} gradually forms during the lifespan of red blood cells. This biochemical process is accelerated in diabetics. The HbA_{1c} level (expressed as a percentage of the hemoglobin) is measured to assess long-term glycemic control.

5. Measurement of the blood glucose level at seven different times during the day.

cemic fluctuations, the HbA_{1c} level and the decrease in complications, confirm that the HbA_{1c} level and the mean blood glucose (MBG) level are credible indicators for predicting long-term complications and dismiss the role of glycemic excursion.

The meaningful indicators of the quality of glycemic control for measuring the long-term consequences of diabetes (complications) are the HbA_{1c} level and the mean blood glucose (MBG) level. The frequency of severe hypoglycemia and that of ketoacidosis are also considered indicators of the quality of glycemic control and of its impact on quality of life.

2.3 GLYCEMIC CONTROL AND LONG TERM COMPLICATIONS

The Diabetes Control and Complications Trial [DCCT Research Group, 1993] is the basis of knowledge about the relationship between glycemic control and the decrease in type 1 diabetic complications. This randomized, controlled trial was conducted between 1983 and 1993 and involved a sample of 1,441 diabetics aged 13 to 39 years. The patients were randomized to two groups that received either conventional therapy (two injections per day) or intensive therapy (four or more injections per day or the insulin pump). For each type of therapy, a primary-prevention cohort (with no signs of complications) and a secondary-intervention cohort (with warning signs of complications) were followed. The purpose of the trial was to determine if tighter glycemic control by means of intensive therapy would reduce microvascular (retinopathy, nephropathy, neuropathy) and macrovascular complications. The DCCT found the improvement in the HbA_{1c} level was better in the intensively treated patients than those receiving conventional therapy. The difference between the two groups was significant throughout the study, the median HbA_{1c} level being 7.07% and 9.02% in the intensive-therapy group and the conventional-therapy group, respectively [DCCT Research Group, 1996].

Most of the patients in the DCCT agreed to participate in a second study, titled Epidemiology of Diabetes Interventions and Complications [EDIC Research Group, 1999]. All the patients (n = 1,375) were offered intensive therapy. The EDIC compared the clinical changes in the original two DCCT cohorts (intensive therapy and conventional therapy) that received intensive therapy during the subsequent eight years (1994 to 2002) [EDIC Research Group, 2002; DCCT/EDIC Research Group, 2000; EDIC Research Group, 1999]. The blood glucose levels were significantly different in the two groups at the start of the EDIC study. However, the difference quickly diminished, and no significant difference in the HbA_{1c} levels was observed during the additional years of follow-up [EDIC Research Group, 2003]. The main conclusions of these two studies are summarized below for each complication.

2.3.1 Microangiopathy

2.3.1.1 Retinopathy

In the patients who had no retinopathy at baseline, intensive therapy decreased the risk of retinopathy by 76% (95% CI: 62 to 85%), whereas in those with preexisting retinopathy, the risk of significant progression of retinopathy was reduced by 54% (95% CI: 39 to 66%) [DCCT Research Group, 1993]. Intensive therapy therefore seems more beneficial if initiated early in the natural course of the disease [DCCT Research Group, 1995a]. However, the investigators observed a temporary deterioration in the retina (6 to 12 months after the start of intensive therapy), which resolved after a longer follow-up (mean of 6.5 years): 54% of the patients experienced sustained progression of retinopathy by three steps of severity (on a scale of 5) with conventional therapy versus 11.5% of the intensively treated subjects in the primary-prevention cohort. In the secondary-intervention cohort, this occurred in 49.2% and 17.1% of the subjects, respectively [DCCT Research Group, 1995c]. The link between the blood glucose level (measured by the HbA_{1c} level) and retinopathy was calculated [DCCT Research Group, 1995d]: for each 10% decrease in the HbA_{1c} level (which decreased, for example,

from 10 to 9% or from 8 to 7.2%), the risk of progression of retinopathy decreased by 45%, regardless of the HbA_{1c} level. The DCCT Research Group [1996] did not find there to be a threshold HbA_{1c} level below which there is no retinopathy. However, according to more recent analyses based on indicators taken from blood glucose profiles, the risk of progression of retinopathy is nonlinear and increases when the mean blood glucose level is above 8.3 mmol/L [Service and O'Brien, 2001].

The follow-up in the EDIC study [EDIC Research Group, 2002] showed that the effect of intensive therapy persisted after six years of follow-up, given that significantly fewer patients in the intensive-therapy group in the DCCT required photocoagulation treatments to prevent vision loss.

2.3.1.2 NEPHROPATHY

The DCCT Research Group [1993] assessed kidney damage through warning signs of increasing severity, such as microalbuminuria, albuminuria, decreased creatinine clearance, and renal failure. The study found a 39% decrease in microalbuminuria and a 54% decrease in albuminuria in the combined cohort. For each 10% decrease in the HbA_{1c} level, the risk of microalbuminuria decreased by 25%. The study did not find there to be a glycemic threshold below which there are no complications [DCCT Research Group, 1996]. However, the EDIC Research Group [2003] examined the progression of microalbuminuria to proteinuria in type 1 diabetes and found that the dose-response relationship was nonlinear. The risk of progression of microalbuminuria to proteinuria is significantly reduced when glycemic control is below an HbA_{1c} level of 8.5%. The natural course of diabetes is accompanied by reversible microalbuminuria and even reversible albuminuria [Friedman, 2003; DCCT Research Group, 1995c], and the variability in the progression of microalbuminuria is not linked solely to the duration of the disease [Allen and Walker, 2003; Perkins et al., 2003]. The follow-up in the EDIC study showed that the effect of intensive therapy on intermediate indicators persisted after eight years: a 59% decrease in the risk of microalbuminuria and an 84% decrease in the risk of clinical-grade albuminuria. After eight years of follow-up, 29.9% of the patients in the intensively treated group had hypertension (a major consequence of nephropathy) versus 40.3% in the conventionally treated group ($p < 0.001$) [EDIC Research Group, 2003]. In addition, fewer patients in the intensively treated group had an elevated serum creatinine level (5 vs. 19; $p = 0.004$), and, despite the small number of events observed, the number of patients who required dialysis or a transplant was 4 versus 7 ($p = 0.36$) in favour of intensive therapy [EDIC Research Group, 2003].

2.3.1.3 NEUROPATHY

The DCCT found a 60% reduction in clinical neuropathy (95% CI: 38 to 74%) in the intensive-therapy group [DCCT Research Group, 1993]. The prevalence of abnormal nerve conduction and autonomic nervous system dysfunction was reduced by 44% (95% CI: 34 to 53%) and 53% (95% CI: 24 to 70%), respectively [DCCT Research Group, 1995f].

Briefly, as regards microangiopathy, studies show that target organ damage is delayed by good glycemic control, but the measurable indicators (HbA_{1c} level and mean blood glucose level) are surrogate outcomes[6] for predicting long-term complications. One cannot rule out the possibility that complications will occur later in the intensively treated group [Shumak, 2004; Chew, 2001]. The risk of progression of retinopathy and nephropathy is significantly reduced below the blood glucose and HbA_{1c} thresholds of 8.3% and 8.5%, respectively.

6 A surrogate outcome is an intermediate outcome used in place of a clinical outcome in a clinical trial and should evolve together with the clinical outcome, be correlated with it quantitatively and be easier to examine than the clinical outcome.

2.3.2 Macroangiopathy

The DCCT Research Group [1995b] observed a nonsignificant decrease in the risk of macroangiopathy of 42% (95% CI: -7 to 68%), or 40 complications with conventional therapy versus 23 complications with intensive therapy (p = 0.08). Macroangiopathy is associated with hyperglycemia, with no apparent threshold [Nosadini and Tonolo, 2004; Coutinho et al., 1999]. The EDIC chose, as an indicator of early macrovascular complications, the measurement of carotid intimal thickness (surrogate outcome for predicting cardiovascular mortality). At the beginning of the study, intimal thickness was identical in three groups (intensive and conventional therapy from the DCCT, and a matched nondiabetic control group). However, at the end of the EDIC, a significant difference in favour of intensive therapy was observed between the diabetics and nondiabetics and between the two DCCT treatment groups, even if their HbA_{1c} levels were not different when they were incorporated into the EDIC study [Nathan et al., 2003].

2.3.3 Glycemic fluctuations and complications

Other authors discuss the effect of blood glucose values measured with daily profiles and of glycemic fluctuations or the postprandial glucose level on the incidence of long-term complications [Buse, 2003; Davidson, 2003]. The link between plasma glucose and HbA_{1c} levels has been reviewed [Rohlfing et al., 2002], but there is no evidence indicating that the magnitude of blood glucose fluctuations leads to complications beyond those that can be predicted by the HbA_{1c} and the mean blood glucose levels [McCarter et al., 2004; Derr et al., 2003].

2.3.4 Other factors associated with the incidence of complications

Since the DCCT, researchers have known that hyperglycemia is not the only factor explaining the occurrence, progression and severity of complications. Other factors have been confirmed, including genetic factors [McCarter et al., 2004; Cohen et al., 2003b; Derr et al., 2003]. Thus, the scientific literature reports new indicators of biological variability correlated with the severity of complications, such as the hemoglobin glycation index (HGI) [McCarter et al., 2004; Derr et al., 2003] and the glycosylation gap (GP) [Cohen et al., 2003b].

For the purposes of this report, only the HbA_{1c} level and the mean blood glucose (MBG) level have been chosen as relevant indicators for the assessment.

2.4 TREATMENT OF TYPE 1 DIABETES

Insulin therapy is the cornerstone of the treatment of type 1 diabetes. Insulin preparations are classified on the basis of their duration of action, onset of action, and peak action time [CDA, 2003]. Up until the publication of the DCCT, insulin therapy was administered conventionally as two daily injections of a mixture of slow- and short-acting insulins. Since the DCCT, intensive therapy by multiple daily injections of slow-acting and short-acting insulin has been recognized as being superior to conventional therapy. A diabetic will therefore have to inject him/herself with a slow-acting basal insulin in the morning or evening (or both if NPH insulin is used) and doses of short-acting insulin before meals and large snacks. The most frequently used slow-acting insulin is neutral protamine Hagedorn (NPH), which has a mean duration of action of 14 ± 3 hours, with peak action occurring three to five hours after injection. An evening injection of NPH insulin will therefore reach its peak of action during the night, when the blood glucose level is low, thereby creating the potential for nocturnal hypoglycemia. Furthermore, NPH insulin is a crystalline suspension that requires vigorous mixing prior to injection. If the mixture is not sufficiently homogeneous, absorption at the injection site will vary, and the effect on the blood glucose level will fluctuate for a given dose and in a given patient. This is why, a few years ago, the industry developed another slow-acting insulin (glargine) with an extended absorption profile over

nearly 24 hours, with no peak action. Insulin glargine is reported to be superior to NPH insulin for fasting glycemic control and in reducing the number of hypoglycemic episodes [Garces et al., 2003; Murphy et al., 2003; Wang et al. 2003; NICE, 2002], although other authors question it [Linne and Liedholm, 2004]. Insulin glargine cannot be mixed in the same syringe as a short-acting insulin, with the result that a separate injection is required. The different treatment modalities are presented in Table 1, including continuous subcutaneous insulin infusion, or the insulin pump, and treatment by multiple daily insulin injections, both of which are intensive therapies. With the pump, the patient does not use a slow-acting insulin but rather a continuous variable infusion of short-acting insulin.

TABLE 1

Treatment modalities for type 1 diabetes

	CONVENTIONAL*	INTENSIVE (BASAL-BOLUS REGIMEN†)	
		MULTIPLE INJECTIONS	INSULIN PUMP
Insulin injections	2/day	4-7/day	Continuous
Route of administration and device	Subcutaneous with syringe or pen	Subcutaneous with syringe or pen	Subcutaneous with pump
Preprandial or postprandial bolus	No	Yes	Yes
Type of insulin			
Slow-acting	NPH	NPH, glargine‡	
Short-acting	Regular	Lispro, regular	Lispro, aspart

Source: Canadian Diabetes Association 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada [Canadian Diabetes Association, 2003].

* Still used occasionally but is no longer preferred since the publication of the DCCT results.

† Intended to mimic pancreatic function, i.e., basal secretion and postprandial secretion.

‡ Insulin glargine has been approved in Canada, but its arrival on the market has been delayed. The Patented Medicines Prices Review Board (PMPRB), a federal agency, approved the selling price requested by the manufacturer (Sanofi) in April 2004 [Source: Sylvie Dupont, secretary of the PMPRB, personal communication, June 2004]. Sanofi is reportedly giving priority to putting insulin glargine on the Canadian market, although no date has been announced.

Before insulin therapy is initiated, all patients should receive initial and ongoing training, including, among other things, detailed information on storing and using insulin, the symptoms and treatment of hypoglycemia (an adverse effect of hyperinsulinemia), adjusting doses on the basis of food intake and physical activity, adjustments during periods of illness, and self blood glucose monitoring. The importance of preventive foot and skin care should be stressed as well.

The dosage should be adjusted on the basis of the therapeutic objectives and on the patient's lifestyle, diet, age, health status, motivation and ability to detect hypoglycemia.

According to the Canadian guidelines, glycemic targets should be individualized, but for most patients (adults and adolescents), treatment should aim for an HbA_{1c} level $\leq 7.0\%$ in order to reduce the risk of complications. In children, glycemic targets vary according to age. They are generally higher (HbA_{1c} level of 8 or even 9%) in order to prevent hypoglycemia [CDA, 2003].

Other types of therapy have been developed as well: artificial pancreas [Bringer et al., 2003; Brunetti et al., 2003; Gin et al., 2003], islet of Langerhans transplantation [Guignard et al., 2004; Hirshberg et al., 2003], inhaled insulin [Clement et al., 2004], and so on, but they are not part of the therapeutic arsenal that is usually used.

3 THE INSULIN PUMP

3.1 DESCRIPTION OF THE TECHNOLOGY

Insulin pump therapy is technically referred to as continuous subcutaneous insulin infusion. It is a method of administering short-acting insulin subcutaneously by means of a portable, battery-operated, programmable infusion pump with a tube and cannula specially designed for this purpose. Insulin is placed in a reservoir inside the pump. The infusion rate is controlled by the pump and is adjustable. As a general rule, the basal infusion rate is maintained 24 hours a day, but the device can be programmed to vary the infusion rate during the day, and the patient can self-administer additional boluses before meals. The pump can be removed temporarily before bathing and physical or sexual activity. In pump users, the cannula is inserted under the skin, where it is kept continually, and attached by a transparent adhesive dressing, usually in the abdominal area. The Teflon or metal cannula is attached to the pump via a tube varying in length from 60 to 110 cm. The patient wears the pump on his/her belt, a bit like a pager. The cannula has to be changed every three days. The tube, as well as the insulin reservoir or cartridge, has to be changed at least every six days. The batteries are replaced as needed, at a frequency varying according to the type of battery. The current pumps incorporate various safety systems for preventing the accidental injection of excess insulin, especially in children, for monitoring pump function (problem with the motor or the battery, maximum daily dose reached, reservoir empty, etc.), or for alerting the patient in the event of an obstruction of the cannula or if the infusion has stopped. A detailed report on the technical characteristics of insulin pumps was published in 2002 by the Emergency Care Research Institute (ECRI)[7]. In 2004, the ECRI also reviewed the minimal technical characteristics that pumps should have.

Advances in pump technology include the integration of various devices, such as a glucose sensor [Hovorka et al., 2004; Steil et al., 2004; Renard, 2003; Renard, 2002; Renard et al., 2002], a bolus calculator [Gross et al., 2003] and a ketone sensor [Guerci et al., 2003].

Basal glycemic control is effected by continuous subcutaneous infusion of short-acting insulin or, in the case of multiple injections, by an injection of slow-acting insulin. In both treatments, the patient has to monitor his/her blood glucose level by measuring it at regular intervals (self-monitoring). With the pump, he/she has to measure his/her blood glucose level at least four times a day (ideally six), and the blood glucose monitoring is more demanding than with multiple injections. The patient programs the injection of additional boluses of short-acting insulin before meals.

7. www.ecri.org/Products_and_Services/Products/Healthcare_Product_Comparison_System/Default.aspx

4 SEARCH METHOD

A search in the International Network of Agencies for Health Technology Assessment (INAHTA) database for previous assessments of insulin pump therapy performed by other agencies in the past decade identified three reports, one prepared in Great Britain [Colquitt et al., 2002] for the National Institute for Clinical Excellence (NICE)[8] (the most recent), and two in Spain [AETS, 2000; Pons, 2000]. One of the three agency reports [AETS, 2000] was excluded because the research question was far broader and because the report mainly concerned the intraperitoneal insulin pump. The conclusions and recommendations of the other two reports are presented in Table A-1 in Appendix A. The other Spanish report [Pons, 2000] notes that there is a paucity of evidence on the efficacy of the insulin pump and on the characteristics of the patients who might benefit from it the most. The report by Colquitt et al. [2002] is an exhaustive report of very high methodological quality that includes the patient perspective. We used its search strategy (see Appendix B) to identify publications postdating their assessment. We chose articles and abstracts published in English, French, Spanish, Italian and German between January 2002 and July 2004. The studies meeting the following criteria were included:

- Intervention: Subcutaneous insulin infusion by pump compared to multiple injection therapy (at least three injections per day).
- Participants: Adults or children with type 1 diabetes. Studies involving pregnant women, newly diagnosed type 1 diabetics, or type 2 diabetics were not included.
- Outcome indicators: HbA_{1c} level, mean blood glucose level, quality of life, adverse effects (severe hypoglycemic episodes, ketoacidotic episodes, etc.).
- Study design: Randomized, controlled trials, randomized cross-over trials, cohort and case series of at least 10 weeks' duration.

Of the 341 articles and other publications identified, 178 were included. After they were read, 56 studies (25 adult and 31 pediatric; details in Section 5.1), two recent meta-analyses and four economic analyses were selected. Great care was taken to avoid data duplication, since some publications present results from overlapping studies. In such cases, only the last study published was included.

In addition to electronic database searches, documents and articles provided by *Diabète Québec* and the support group *GlucoMaîtres* were manually searched to identify articles meeting our criteria during the period of interest.

The safety profile was determined from assessment agency reports, articles from scientific journals, recent publications (after January 2002) and information from national incident report databases (United States, Great Britain and Canada).

The cost data were taken from various sources and are detailed in Chapter 8. Information on coverage of the technology in Canada and elsewhere in the world is from the scientific literature and a targetted Internet search, as well as from *Diabète Québec*.

The patient and health professional perspectives were explored by means of a survey and interviews. Various groups representing patients and clinical settings, recruited with the help of *Diabète Québec*, participated. Patients and parents of children who were using or who wanted to use the pump were invited to give their comments by means of a self-administered semi-open-ended questionnaire. Teams of health professionals were met with during one- to two-hour semidirected interviews. The results of the questionnaire and interviews are presented in Chapters 6 and 7, which concern the patient and health professional perspectives.

8. The NICE guidelines [2003] are available on the Internet, as is Colquitt and colleagues' report [2002], on which NICE bases its conclusions. This report was recently published in a technology assessment journal [Colquitt et al., 2004].

5 RESULTS OF THE SCIENTIFIC LITERATURE REVIEW

5.1 STUDY SELECTION

5.1.1 Clinical studies involving adult diabetics

Many adult studies on the use of the insulin pump have been published since Colquitt and colleagues' literature review [2002] (25 publications, including 15 studies and 10 abstracts) (see description of the studies in Tables A-2, A-3 and A-4 in Appendix A).

Three randomized, controlled trials (one published trial and two abstracts) were selected [DeVries et al., 2002; Bode et al., 2003; Bolli et al., 2004] (Table A-2, Appendix A). Ten studies were considered separately because of a less robust study design (retrospective or prospective cohort studies or case series with no control group) [Garg et al., 2004; Garmo et al., 2004; Lepore et al., 2004; de Borst and Berghout, 2003; Hunger-Dathe et al., 2003; Hissa et al., 2002; Bruttomesso et al., 2002; Cersosimo et al., 2002; Linkeschova et al., 2002; Rudolph and Hirsch, 2002] (Table A-3, Appendix A).

Twelve publications were excluded (five studies and seven abstracts) for one of the following reasons: 1) the objective of the study was not to compare the pump with multiple injections [Kamoi et al., 2004; Armstrong and King, 2002; Bode et al., 2002b; Meyer et al., 2002; Catargi et al., 2001]; 2) the pump was offered to newly diagnosed patients or to a particular clientele [Lenhard and Maser, 2003; Pozzilli et al., 2003]; or 3) the pertinent results concerning glycemic control or the duration of follow-up are not provided [Harmel and Mathur, 2004; Hayes et al., 2003; King and Armstrong, 2003; Mathur and Harmel, 2003; Mathur et al., 2002] (Table A-4, Appendix A).

5.1.2 Clinical studies involving diabetic children

Many studies on the use of the insulin pump in children have been published since Colquitt and colleagues' literature review [2002] (31 publications, including 20 studies and 11 abstracts) (see description of the studies in Tables A-5, A-6 and A-7 in Appendix A).

Five randomized, controlled trials (three published trials and two abstracts) were selected [Doyle et al., 2004; Cohen et al., 2003a; Weintrob et al., 2003 and 2004a; Wilson et al., 2003; Fox et al., 2002] (Table A-5, Appendix A). Sixteen studies were considered separately because of a less robust study design (retrospective or prospective cohort studies or case series with no control group) (Table A-6, Appendix A).

Ten publications were excluded (five studies and five abstracts) for one of the following reasons: 1) the objective of the study was not to compare the pump with multiple injections [Burdick et al., 2004; Heptulla et al., 2004; Humphrey et al., 2004; Schiaffini et al., 2002]; 2) there were fewer than five subjects [Razeghi et al., 2002]; 3) the pump was offered to children who were newly diagnosed with type 1 diabetes [Quinn et al., 2003; Ramchandani, 2003; Pozzilli et al., 2003]; or 4) the pertinent results concerning glycemic control are not provided [Hofer and Steichen, 2003; Pinsker et al., 2003] (Table A-7, Appendix A).

5.2 SAFETY

Safety will be assessed in terms of the theoretical risks and pump technical malfunction reports. Pump malfunction can result in an underinfusion or an overinfusion of insulin leading to severe hypoglycemia (requiring immediate assistance) or ketoacidosis and diabetic coma. Since ketoacidosis and hypoglycemia can also result from suboptimal diabetes management on the part of a patient on intensive therapy, whether by injection or by pump, they cannot automatically be interpreted as being caused by a pump malfunction.

5.2.1 Technical problems and incidents

Since it came onto the scene in 1976 [CDA, 2003; Pickup and Keen, 2002], the insulin

pump has evolved tremendously in size, weight, functionality and complexity. At the beginning, the scientific literature reported numerous technical problems posing a risk of insulin underinfusion that could go unnoticed and a risk of overinfusion. Today, pumps are equipped with alarm systems that signal various malfunctions. The risk of the cannula inserted under the skin dislodging unbeknownst to the patient—a situation that can quickly degenerate into ketoacidosis—still exists. Patients who use a pump should therefore self-monitor their blood glucose level very diligently.

A study cited in Colquitt and colleagues' report [2002] links ketoacidosis to a technical problem with the pump. Other studies mention problems with the cannula dislodging. In their systematic review, Weissberg-Benchell et al. [2003] identify 11 studies—all of which were conducted before 1988—that report technical problems with the pump and seven studies reporting cannula occlusions.

In 2003, Health Canada ordered a recall of a model of pump that was found to be defective when in contact with water. As regards Health Canada's incident report database, the Health Products and Food Branch (HPFB) received six incident reports in three years. The incidents were not found to be linked to a defect in the pump, but rather to improper patient use[9]. In the United States, 48 deaths in pump users were reported to the Food and Drug Administration [2003] between 1998 and 2003[10]. One-half of these deaths occurred in the past year. Each incident was detailed and investigated, but not thoroughly analyzed[11]. Consequently, these deaths cannot be attributed to pump malfunction. In Great Britain, the Medicines and Health-care Products Regulatory Agency (MHRA) responsible for monitoring incidents informed us that, in the past ten years, it had received 97 incident reports concerning the insulin pump, including 82 involving overinfusion[12]. After an investigation, malfunction was linked to the pump per se in 6% of the cases. Information on the impact of these incidents on health is not presently available. Closer to home, in Toronto, a study conducted in a pediatric setting found that 23% of the children who were using a pump experienced a technical problem whereby the pump had to be replaced. However, the nature and severity of the impact of such incidents on health are not mentioned [Liberatore et al., 2004].

It therefore seems that the insulin pump is still prone to technical problems, but the nature and severity of their impact on the patients' health cannot be accurately assessed.

5.2.2 Severe hypoglycemic episodes

As indicated by the DCCT Research Group [1995e] and by a more recent meta-analysis of randomized, controlled trials [Egger et al., 1997], intensive therapy, regardless of the modality (pump or multiple injections), leads to adverse effects, such as severe hypoglycemic episodes, more frequently than conventional therapy. Hypoglycemia can be mild, moderate or severe (requiring outside assistance), according to the classifications in the scientific literature. In their report, Colquitt et al. [2002] state that, on the whole, randomized, controlled trials show no difference in the incidence of severe hypoglycemic episodes between pump-treated patients and those treated by multiple injections, but that observational studies report fewer severe hypoglycemic episodes in pump-treated patients. The authors of another systematic literature review [Weissberg-Benchell et al., 2003] indicate that the risk of severe hypoglycemic episodes is not higher with the pump: 10 studies found no difference, 7 found fewer such episodes with the pump, and just one study reports more with the pump. The recent adult and pediatric studies identified in connection with this report concur with Colquitt et al. [2002]. The observation is as follows: both in children and adults, randomized, controlled trials do not indicate any difference in the

9. Martine Vallerand, inspector, HPFB, personal communication, October 2003.

10. The number of pump users during this period is not known. As an estimate, Colquitt et al. [2002] mention, in their report, 140 000 users in the United States in 2002, according to INPUT (INsulin PUmp Therapy), a British advocacy group that recommends the use of the pump.

11. Among other things, the database does not indicate if these deaths occurred in individuals who were recent pump users.

12. Jim Lefever, technical adviser, MHRA, personal communication, June 2004.

incidence of severe hypoglycemic episodes, and nonrandomized studies report fewer such episodes with the pump. This can be explained by the choice of patients in nonrandomized studies, where pump therapy is proposed to those who might benefit from it the most. As for the few recent studies that compared pump therapy and multiple injection therapy with glargine, the sample size in the randomized, controlled trials was too small to permit any conclusions, and the nonrandomized studies showed no difference in the incidence of severe hypoglycemic episodes between the pump and multiple injections with glargine. Two studies, one involving adults selected at the beginning of the study [Lepore et al., 2004], the other involving children [Alemzadeh et al., 2004] show that the pump and multiple injections with glargine are more effective than multiple injections with NPH in reducing the incidence of severe hypoglycemic episodes.

5.2.3 Ketoacidosis

In their report, Colquitt et al. [2002] state that studies show no difference in the incidence of ketoacidotic episodes between pump-treated patients and those treated by multiple injections, and that there were a greater number of such episodes in older studies. This is also the opinion of Weissberg-Benchell et al. [2003], who note that, prior to 1993, six studies reported more ketoacidotic episodes with the pump and that after 1993, two of four studies reported the same number. In their meta-analysis of randomized, controlled trials of the risks accompanying intensive therapy compared to conventional therapy, Egger et al. [1997] note seven times more ketoacidotic episodes (odds ratio [OR]: 7.2; 95% CI: 2.95 to 17.58) in the pump-only trials and a 13% increase in the risk of ketoacidosis (OR: 1.13; 95% CI: 0.15 to 8.35) in the multiple injections-only trials. However, all but one of the trials involving pump therapy were conducted before 1990. They also mention an analysis by the DCCT Research Group [1995a] of the adverse effects observed during intensive therapy that indicates a significant increase in ketoacidotic episodes with the pump. The sample size in the more recent randomized, controlled trials, both adult and pediatric, is too small to permit any conclusions. However, despite the fact that there was no significant difference, most of the trials noted a higher absolute number of ketoacidotic episodes with the pump than with multiple injections.

It therefore seems that ketoacidotic episodes were more frequent with the first generations of pumps, but that they occurred less often in the more recent studies. However, they are more frequent with the pump than with multiple injections.

5.2.4 Other adverse effects

Colquitt and colleagues' report [2002] notes that studies provide little information about adverse effects other than ketoacidosis and severe hypoglycemia. The other adverse effects reported in studies include, among others: subcutaneous and cutaneous infections or abscesses at the cannula insertion site [Weissberg-Benchell et al., 2003], lipoatrophy [Ampudia-Blasco et al., 2003; Griffin et al., 2001], lipohypertrophy [Sulli and Shashaj, 2003], potentially hypoglycemia-induced traffic accidents [Harsch et al., 2002] and, possibly, vitiligo [Burge and Carey, 2004].

5.3 EFFICACY

As regards therapeutic efficacy, the only glycemic indicators associated with long-term complications for which there are data are the HbA_{1c} level and the mean blood glucose level. Although they are intermediate indicators (surrogate outcomes), the efficacy of the pump will be assessed in terms of its ability to significantly lower the HbA_{1c} level or the mean blood glucose level compared to multiple injection therapy. Reports and previous studies have raised another point, the possible and potentially significant impact of the pump on quality of life, especially in patients with wide glycemic fluctuations. Quality-of-life indicators were recently incorporated into a scale validated for diabetes, and the results of the recent studies that refer to it will be reviewed.

5.3.1 HbA_{1c} level, mean blood glucose level and glycemic control

5.3.1.1 META-ANALYSES CONCERNING GLYCEMIC CONTROL

Three meta-analyses were identified, two of which are relevant (presented in Table A-8 in Appendix A) [Colquitt et al., 2002; Pickup et al., 2002]. The quality of these meta-analyses was assessed using a grid designed for this purpose. The grid includes various criteria, such as the quality of the literature search method, the rigour of the criteria for including trials on the basis of their methodological quality, of the review-and-agreement process between the investigators, of the quantitative and statistical methods, and of the sensitivity studies performed, and the degree to which the conclusions follow from the results. In 2002, Pickup (one of the fathers of the insulin pump) published a meta-analysis including 12 randomized, controlled trials, eight of which were similar to Colquitt's meta-analysis. Pickup and colleagues' meta-analysis concludes that glycemic control was better with the pump and that there was significantly greater glycemic variability with multiple injections. The mean blood glucose level in the pump-treated patients was 1.06 mmol/L (0.88 to 1.34 mmol/L) lower, and the HbA_{1c} level was 0.51% lower[13]. The clinical significance of this slight improvement is difficult to assess. The authors postulate that there would be a 5% decrease in retinopathy after 10 years and conclude that the pump is an effective tool for improving glycemic control. However, the pump is not necessary for all type 1 diabetics and should be reserved for those who experience specific problems with injection therapy [Pickup et al, 2002].

Colquitt and colleagues' meta-analysis [2002], upon which the NICE guidelines [2003] are based, presents the results of 14 adult studies at various lengths of follow-up (ten weeks to one year) and shows a significant improvement in the HbA_{1c} level (- 0.84%; 95% CI: - 1.59 to - 0.16) after four months of follow-up (including only randomized, controlled trials), but not at six months of follow-up. The all-study meta-analysis found no significant difference, and this at any length of follow-up. On average, the HbA_{1c} level was 0.6% lower (- 0.61; 95% CI: - 1.29 to 0.07) with the pump than with multiple injections at one year. Two randomized, controlled trials involving adolescents had been identified, and no pediatric studies meeting the inclusion criteria had been found at the time.

A third meta-analysis of 52 studies of the efficacy of the insulin pump compared to multiple injections or conventional therapy in improving glycemic control has been published [Weissberg-Benchell et al., 2003]. Unfortunately, the authors do not perform a separate analysis for comparing the pump and intensive therapy alone. Most analyses compare studies of the pump with all studies of intensive therapy and conventional therapy grouped together. The authors state that the improvement in the HbA_{1c} level was superior for patients who went from conventional therapy to the pump than for those who were treated with multiple injections (although this improvement was not quantified for multiple injections). As for the mean blood glucose level, the authors report a nonsignificant improvement with the pump compared to multiple injections (158.76 ± 10.99 vs. 139.12 ± 7.09 mg/dL; $p = 0.186$[14]) in the case series (pre- and post-pump). The other results presented do not permit a comparison between the pump and multiple injections.

The three meta-analyses report the same limitations: most of the clinical studies were conducted more than 15 years ago and therefore examined now-obsolete technologies; the type of insulin used with the pump has changed in the past 20 years; and the type of intensive therapy with injections varied widely from study to study. The study inclusion criteria vary according to the evaluation of the methodological quality. Weighting based on methodological quality is not clear in two of the three meta-analyses. Colquitt and colleagues' comparison [2002], that is, the efficacy of the pump versus multiple injections, its methodo-

13. All the HbA_{1c} values cited in this report are absolute values.

14. Or 8.81 ± 0.61 mmol/L versus 7.72 ± 0.39 mmol/L. The glycemic control indicators in the 2003 Canadian guidelines are expressed in mmol/L (international units). The factor for converting from mg/dL (conventional units) to mmol/L is 0.05551.

logical quality and the rigour of the discussion make it the meta-analysis that provides the most informed answer to the question asked by Québec policymakers.

5.3.1.2 Recent adult studies

Of the three randomized, clinical trials published since Colquitt and colleagues' report [2002], one compares the efficacy of the pump with that of multiple injections with NPH, while the other two compare it with that of multiple injections with glargine (also referred to as the "poor man's pump").

Multiple injections with NPH

In the only randomized, controlled trial (n = 79) comparing the pump and multiple injections with NPH that was identified, DeVries et al. [2002] observed a significant improvement in the HbA_{1c} level with the pump after four months of follow up (0.84%; 95% CI: - 1.31 to - 0.36; $p = 0.002$) compared to multiple injection therapy with NPH in patients with poor glycemic control (HbA_{1c} level ≥ 8.5%). The mean blood glucose level was not, however, significantly different between the two groups (Table 2).

The two nonrandomized, controlled studies that we identified [Cersosimo et al., 2002; Hissa et al., 2002] report a significant difference in the improvement in the HbA_{1c} level with the pump at one year of follow-up (Table 3).

TABLE 2

Efficacy of insulin pump therapy compared to multiple injections with NPH: randomized, controlled adult trial

TRIAL	HbA_{1c} LEVEL (%)		
	INSULIN PUMP	MULTIPLE INJECTIONS WITH NPH	DIFFERENCE BETWEEN THE PUMP AND MULTIPLE INJECTIONS WITH NPH
DeVries et al., 2002 N = 79 Duration: 4 months	Before-after difference - 0.91 ± 1.28%	Before-after difference - 0.07 ± 0.70%	0.84% (95% CI: - 1.31 to - 0.36) p^* = 0.002

* Statistical significance of the difference between the pump-treated group and the group treated by multiple injections with NPH

TABLE 3

Efficacy of insulin pump therapy compared to multiple injections with NPH: nonrandomized, controlled adult studies

STUDY	HbA_{1c} LEVEL (%)		
	INSULIN PUMP	MULTIPLE INJECTIONS WITH NPH	p*
Cersosimo et al., 2002 (abstract) N = 85 Duration: 24 months	**Before:** 8.0 ± 1.2 **After:** 7.1 ± 1.1 **Difference**: - 0.9	**Before:** 8.6 ± 1.6 **After:** 8.1 ± 1.0 **Difference**: - 0.5	< 0.05
Hissa et al., 2002 N = 29 Duration: 18 months	**Before:** 8.3 ± 1.1 **After:** 6.5 ± 0.5 **Difference** : - 1.8 ($p < 0.001$)	**Before:** 7.6 ± 0.8 **After:** 7.5 ± 0.5 **Difference** : - 0.1 (NS†)	< 0.001

* p: Statistical significance of the difference between the pump-treated group and the group treated by multiple injections with NPH.
† NS: Difference not significant.

The six case series that describe the clinical outcomes of replacing multiple injections with pump therapy report a significant difference in glycemic control before and after treatment [Garmo et al., 2004; de Borst and Berghout, 2003; Hunger-Dathe et al., 2003; Bruttomesso et al., 2002; Linkeschova et al., 2002; Rudolph and Hirsch, 2002]. In these studies, the improvement in the HbA_{1c} level varied from 0.1 to 1.8%. The duration of follow-up in most of the studies was at least 12 months. All of the nonrandomized studies are subject to selection bias, particularly the case series, which included patients who met specific criteria and who were thus selected because the pump could be of benefit to them.

Multiple injections with glargine

Four studies comparing the pump and multiple injections with glargine were identified (Table 4). Two of these studies measured the HbA_{1c} and the mean blood glucose levels [Bolli et al., 2004, Lepore et al., 2004], one of them measured only the HbA_{1c} level [Garg et al., 2004], and the fourth one measured only the mean blood glucose level [Bode et al., 2003]. One of the two randomized, controlled trials [Bolli et al., 2004] found no difference between the pump and multiple injections with glargine in improving the HbA_{1c} level or the mean blood glucose level. The other [Bode et al., 2003], a 5-week, randomized, crossover trial, reports a significant difference in the mean blood glucose level (area under the curve) with continuous blood glucose monitoring in favour of the pump. These trials are available only as abstracts. Two cohort studies that compared the pump and multiple injections with glargine [Garg et al., 2004; Lepore et al., 2004] found no significant difference in the HbA_{1c} level. One of the studies [Lepore et al., 2004] provides the results of daily blood glucose profiles. The mean blood glucose was similar, but the mean amplitude of glycemic excursion (MAGE) points to significantly less glycemic fluctuation with the pump.

Summary (adults)

Studies comparing the pump and multiple injections with NPH found that the pump is slightly superior in terms of metabolic control, particularly in the groups with inadequate glycemic control at baseline (HbA_{1c} level ≥ 8.5%). The randomized and the nonrandomized studies comparing the pump and multiple injections with glargine found no significant improvement in the HbA_{1c} level with pump therapy.

TABLE 4

Efficacy of insulin pump therapy compared to multiple injections with glargine: randomized and nonrandomized, controlled adult studies

STUDY*	HbA_{1c} LEVEL (%)		
	INSULIN PUMP	MULTIPLE INJECTIONS WITH GLARGINE	p†
Bolli et al., 2004 RCT (abstract) N = 57 Duration: 6 months	**Before:** 7.7 ± 0.7 **After:** 7.0 ± 0.8 **Difference:** - 0.7	**Before:** 7.8 ± 0.6 **After:** 7.2 ± 0.7 **Difference:** - 0.6	NS‡
Garg et al., 2004 Retrospective cohort study N = 515 Duration: = 12 months	**Before:** 7.7 ± 0.1 **After:** 7.5 ± 0.1 **Difference:** - 0.2 ($p < 0.001$)	**Before:** 8.0 ± 0.1 **After:** 7.7 ± 0.1 **Difference:** - 0.3 ($p < 0.001$)	NS
Lepore et al., 2004 Prospective cohort study N = 48 Duration: 12 months	**Before:** 9.0 ± 1.3 **After:** 8.0 ± 1.0 **Difference**: - 1.0 ($p < 0.001$)	**Before:** 8.6 ± 1.1 **After:** 7.9 ± 1.2 **Difference**: - 0.7 ($p < 0.001$)	NS

* The study by Bode et al. [2003] was not included in this table because they did not examine HbA_{1c} levels.
† p: Statistical significance of the difference between the pump-treated group and the group treated by multiple injections with glargine.
‡ NS: Difference not significant.

5.3.1.3 RECENT PEDIATRIC STUDIES

Multiple injections with NPH insulin

None of the four randomized trials comparing the pump and multiple injections with NPH that were identified found a difference between the pump and multiple injections with NPH with regard to improving the HbA_{1c} level. Two of these studies involved children under the age of the 6 years [Wilson et al., 2003; Fox et al., 2002], one children aged 8 to 14 years [Weintrob et al., 2003] and one youths aged 14 to 18 years [Cohen et al., 2003a] (Table 5).

When this report was published, a randomized, controlled trial involving preschoolers had just been published [DiMeglio et al., 2004b]. Its results confirm those of the other studies, i.e., that there is no difference between the pump and multiple injections with NPH in terms of glycemic control.

A single parallel-group cohort study with a very small sample (n = 12) was identified. It found no difference between the pump and multiple injections in the children under the age of 3 years [Rami et al., 2003] (Table 6).

TABLE 5

Efficacy of insulin pump therapy compared to multiple injections with NPH: randomized, controlled pediatric trials

TRIAL	HbA_{1c} LEVEL (%)		
	INSULIN PUMP	MULTIPLE INJECTIONS WITH NPH	*P**
Cohen et al., 2003a N = 16 Duration: 12 months	**Before:** 8.58 ± 0.82 **After:** 8.15 ± 1.3 **Difference:** - 0.5	**Before:** 8.48 ± 1.4 **After:** 8.57 ± 0.44 **Difference:** - 0.1	NS†
Weintrob et al., 2003 N = 23 Duration: 3.5 months	**Before:** 8.0 ± 1.1 **After:** 8.0 ± 0.7 **Difference:** 0	**Before:** 8.3 ± 0.7 **After:** 8.1 ± 0.8 **Difference:** - 0.2	NS
Fox et al., 2002‡ (abstract) N = 10 Duration: 6 months	**Before:** 8.0 ± 0.4 **After:** 7.57 ± 0.19 **Difference:** - 0.4	**Before:** 7.9 ± 0.6 **After:** 7.17 ± 0.33 **Difference:** - 0.7	NS
Wilson et al., 2003 (abstract) N = 16 Duration: 28 weeks	**Before:** 8.0 ± 1.1 **After:** 7.6 ± 0.8 **Difference:** - 0.4	**Before:** 7.8 ± 1.0 **After:** 7.6 ± 0.7 **Difference:** - 0.2	NS

* *p*. Statistical significance of the difference between the pump-treated group and the group treated by multiple injections with NPH.
† NS: Difference not significant.
‡ Pump compared with standard treatment with insulin injections.

TABLE 6

Efficacy of insulin pump therapy compared to multiple injections with NPH: nonrandomized, controlled pediatric study

STUDY	HbA_{1c} LEVEL (%)		
	INSULIN PUMP	MULTIPLE INJECTIONS WITH NPH	*P**
Rami et al., 2003 Retrospective cohort study‡ N = 12 Duration = 24 months	**Before:** 8.5 (6.8-11.3) **After:** 7.3 (6.4-8.7) **Difference:** - 1.2	**Before:** 8.3 (8.0-10.1) **After:** 7.0 (5.1-10.1) **Difference:** - 1.3	NS†

* *p*. Statistical significance of the difference between the pump-treated group and the group treated by multiple injections with NPH.
† NS: Difference not significant.
‡ Experimental group: Recent diagnosis, pump therapy; control group: patients receiving conventional therapy.

Fourteen studies were case series (pre- and post-pump). Ten of them report that the pump had a significant effect on the HbA_{1c} level [Liberatore et al., 2004; Shehadeh et al., 2004; Pankowska et al., 2003; Plotnick et al., 2003; Schiaffini, 2003; Sulli and Shashaj, 2003; Weinzimer et al., 2003; Willi et al., 2003; Buckloh et al., 2002; Litton et al., 2002], while four found no significant effect on the HbA_{1c} level [Steijlen et al., 2004; Hathout et al., 2003; Saha et al., 2002; Tumini et al., 2002]. The before-after difference in the HbA_{1c} level varied from - 1.3 to - 0.46%. The study involving children who had been selected because they were having problems with glycemic control found a difference of - 1.5% in the HbA_{1c} level [Litton et al., 2002]. Three studies [Steijlen et al., 2004; Sulli and Shashaj, 2003; Tumini et al., 2002] had a duration of follow-up of less than 12 months. The two studies [Hathout et al., 2003; Sulli and Shashaj, 2003] that give the mean blood glucose levels found no difference between the two treatments. The study by Weintrob et al. [2004b] reports a larger area under the postprandial hyperglycemia curve with multiple injections ($p = 0.03$), but the 24-hour hyperglycemia curve was identical for both treatments.

Multiple injections with glargine

In a randomized, controlled trial involving 32 children, Doyle et al. [2004] found an improvement in glycemic control in youths aged 8 to 19 years who were treated with the pump compared to the group treated by multiple injections with glargine (Table 7). The duration of follow-up was short (four months), and the improvement in the HbA_{1c} level was 1%. An examination of the daily blood glucose profiles revealed an identical glycemic improvement in the morning, but the presupper blood glucose levels were higher with multiple injections with glargine. To explain this, the authors postulate that there was, in the youths treated by multiple injections, poorer compliance in administering their insulin injections before their afternoon snacks. The pump has a bolus history memory function (which is not possible with multiple injections), thanks to which the clinician can stress the importance of presnack boluses.

The only other study (n = 80) that has compared the pump and multiple injections with glargine with previous treatment with multiple injections of NPH selected the group of pump-treated patients because they were highly motivated [Alemzadeh et al., 2004]. The pump significantly reduced HbA_{1c} levels after 12 months of follow-up, while insulin glargine improved HbA_{1c} levels only in a subgroup of patients. The improvement in HbA_{1c} levels observed in this study was smaller than that in Doyle's study (Table 7).

Summary (children)

Recent studies comparing the pump and multiple injections with NPH found that the pump can improve glycemic control, but that this improvement is not significant. The corpus of nonrandomized, controlled studies comparing the pump and multiple injections with NPH confirms that the pump can have a beneficial effect on glycemic control in children, but that the significance and extent of this effect depend on the study population. Studies comparing the pump and multiple injections with glargine report a significant improvement with the pump. This does not mean that the pump is superior to multiple injections, since only a randomized trial comparing the three treatments (pump, multiple injections with glargine and multiple injections with NPH) could answer this question.

TABLE 7

Efficacy of insulin pump therapy compared to multiple injections with glargine: randomized and non-randomized, controlled pediatric studies

STUDY	HbA_{1c} LEVEL (%)		
	INSULIN PUMP	MULTIPLE INJECTIONS WITH GLARGINE	*P**
Doyle et al., 2004 RCT N = 32 Duration: 4 months	**Before:** 8.1 ± 1.2 **After:** 7.2 ± 1.0 **Difference:** - 0.9 ($p < 0.02$)	**Before:** 8.2 ± 1.1 **After:** 8.1 ± 1.2 **Difference:** - 0.1	< 0.05
Alemzadeh et al., 2004 Cohort study N = 80 Duration: 12 months	**Before:** 8.4 ± 1.0 **After:** 7.8 ± 0.8 **Difference:** - 0.6 ($p < 0.002$)	**Before:** 8.5 ± 1.1 **After:** 8.2 ± 0.9 **Difference:** - 0.3 (NS†)	Not indicated

* *p*: Statistical significance of the difference between the pump-treated group and the group treated by multiple injections with glargine
† NS: Difference not significant.

5.3.2 Systematic reviews of the literature on quality of life

The Diabetes Quality of Life (DQOL) questionnaire measures the impact of diabetes on the different domains of daily life. It includes 46 items divided into four categories (life satisfaction, diabetes impact, worries about diabetes, and social/vocational concerns) [DCCT Research Group, 1988]. The Diabetes Quality of Life for Youth (DQOLY) is a version of the DQOL adapted for youth. More-detailed instruments were recently developed, such as the Audit of Diabetes-Dependent Quality of Life (ADDQoL) and the Diabetes Treatment Satisfaction Questionnaire (DTSQ) [Bradley and Speight, 2002], but little use of them is made in the literature that was identified.

Colquitt et al. [2002] identified only one study [Tsui et al., 2001] that used the DQOL. The study in question found no significant difference between the two treatments (pump and multiple injections). They examined the published quality-of-life instruments and their strengths and weaknesses, and determined the extent to which they reflect the concerns expressed by patients. Weissberg-Benchell et al. [2003] identified five studies that used a quality-of-life instrument. Two of them found a significant change in favour of the pump, but the patients' age and the instruments used are not mentioned.

5.3.2.1 Recent studies

Adult

Since Colquitt and colleagues' literature review [2002], there has been no new evidence, from randomized or cohort studies in the general population of type 1 diabetics, regarding the improvement in quality of life. DeVries et al. [2002] found a significant improvement in certain aspects of quality of life (general health and mental health) in adults with long-standing poor glycemic control, using the Medical Outcome Study 36-Item Short-Form Survey (SF-36), which measures eight quality-of-life domains.

Linkeschova et al. [2002] measured quality of life with the 64-item Diabetes-Specific

Quality-of-Life-Scale (DSQOLS), which was developed by Bott et al. [1998]. This study, which involved a series of selected cases, found a significant improvement in the DSQOLS scores after pump therapy.

None of the studies that compared the pump and multiple injections with glargine examined quality of life.

For the general population of type 1 diabetics, there is no evidence from randomized, controlled trials or cohort studies indicating the effect of the pump on quality of life. The two recent adult studies that compared the pump and multiple injections with NPH in patients selected because of inadequate glycemic control report a significant improvement in various aspects of quality of life with the pump.

Pediatric

Four of the five randomized trials that examined quality of life using the DQOLY [Doyle et al., 2004; Weintrob et al., 2003; Wilson et al., 2003; Fox et al., 2002], including the trial with multiple injections with glargine as the comparator treatment, found no difference in quality of life between the two treatments. A trial involving youths aged 14 to 18 years [Cohen et al., 2003a] found a significant improvement in certain aspects of quality of life. This trial examined only three aspects of the DQOLY instrument: satisfaction with treatment, worry, and the impact of the disease. The authors report a significant improvement in satisfaction, while results for the other two aspects were similar.

Two case series have measured quality of life. One of them [Buckloh et al., 2002] observed no difference before and after pump therapy, but the instrument used is not mentioned in the abstract. The other [Shehadeh et al., 2004] used a modified DQOL scale with 19 questions divided into two subcategories (impact on the child and impact on the parents) and reports an improvement with the pump.

Most studies have not found a significant effect on the quality of life of pediatric pump users, but one randomized, controlled trial reports that pump therapy seems to improve satisfaction with treatment (DQOLY subset).

5.3.3 Patient selection criteria

According to the scientific literature, the pump is more effective for selected patients. The only evidence-based criterion for selecting patients who are likely to benefit from the pump is that which DeVries et al. [2002] used in a recent randomized, controlled trial, which found that pump therapy led to a significant improvement in the health of patients with long-standing poor glycemic control ($HbA_{1c} \geq 8.5\%$). Table C-1 in Appendix C lists the various indications and various coverage criteria proposed in the NICE guidelines [2003] and by third-party payers. Table C-2 lists patient selection criteria proposed by authors of journal articles or of recent clinical studies.

Various criteria for selecting adult patients who are likely to benefit from the pump are thus proposed, but these expert opinions are not evidence-based. There seems to be a general consensus regarding some of the criteria for determining the limited, selected group that would benefit from the insulin pump:

- Inadequate glycemic control, despite a trial with intensive insulin therapy, if possible, with insulin glargine (patient already self-administering four to seven injections a day and having received excellent basic education on intensive insulin therapy by injections). The starting HbA_{1c} value at which the pump might be recommended varies according to the author and expert

and according to the patient's age group (HbA_{1c} level of 6.5 to 9%);

- Recurrent, unpredictable, severe hypoglycemic episodes (two or more a year), nocturnal hypoglycemia or hypoglycemia unawareness, causing incapacitating anxiety and affecting the quality of life;
- Morning hyperglycemic episodes (morning blood glucose level of 8 or 9 mmol/L).

For children, the criteria are the same, plus:

- Extreme insulin sensitivity, i.e. < 20 units of insulin per day.

In addition, the patient or his/her family should have the following characteristics:

- Measures his/her blood glucose level at least four times a day;
- Is motivated and serious when trying the pump;
- Does not have any false hopes or illusions regarding the pump;
- Has the ability to learn to use the pump and to adjust his/her insulin doses;
- Is able to communicate with the treatment team and exhibit good therapeutic compliance.

A patient screening tool, which efficacy and cost-effectiveness were evaluated, was identified in the literature. Sanfield et al. [2002], after noting during a scientific literature review covering the previous ten years that the discontinuation rate with the pump was greater than 50% two years after pump therapy was initiated, developed a tool for selecting suitable candidates for the insulin pump and evaluated its efficacy and cost. The proposed selection tool is actually a trial period. To patients who wanted to improve their blood glucose levels, they offered to replace their current treatment with the pump. The patients were selected during three visits totaling five hours over a 2-month period, and by means of a trial with a pump infusing a saline solution for three to five days. In the end, 35% of the 104 subjects turned down pump therapy, with full knowledge of the facts. In the subjects who continued pump therapy for more than two years, the authors observed a discontinuation rate of only 3.3%. The other candidates successfully continued intensive therapy with the pump at lower costs than those reported by the DCCT.

The various authors and third-party payers who use selection criteria all stress the importance of the patient understanding, but the scientific literature does not offer any measuring instruments or indicators of this understanding.

Likewise, the experts point out various contraindications, which vary according to the clinical setting. Those mentioned most often are advanced diabetic complications (active retinopathy requiring laser treatment; nephropathy with a serum creatinine level > 150 µmol/L), abnormal liver function, insulin resistance, alcohol or other drug abuse, heart disease, uncontrolled hypertension, allergy to insulin, and psychological problems.

6 THE PATIENT PERSPECTIVE

To understand the arguments in favour of using the pump, it is important to understand the viewpoint of adults, but also that of parents of diabetic children who use or would like to use it (see Chapter 4 – Search Method). We therefore conducted a survey, which was answered, on a voluntary basis, by 23 adults in a support group—at a university hospital (Royal Victoria) in Montreal—for patients on insulin pump therapy and by 11 people in a support group for parents of children on pump therapy (*GlucoMaîtres*) in the Quebec City area. Thirty-four people answered our survey—30 users[15] and 4 would-be users. The questionnaire, which is shown in Appendix D[16], includes closed-ended and open-ended questions of a qualitative nature.

Since the sample was small, these comments cannot be generalized to all type 1 diabetics who are using or previously used the pump. Sociodemographic data on the survey's respondents are presented in Table D-1 in Appendix D.

6.1 BENEFITS AND LIMITATIONS OF THE PUMP

6.1.1 Benefits

As regards adults, the survey's participants were very much in favour of the pump. All the users wanted to continue with pump therapy, and 3 of the 4 nonusers wanted to adopt it. The parents of diabetic children were highly motivated, and all of them wanted their children to continue with pump therapy. The answers to the open-ended questions suggest that the participants had a good knowledge of diabetes and its daily management and organized themselves to deal with this.

The main reasons that had led the patients to switch from multiple injections to the insulin pump and the improvements observed after pump therapy was started are presented in Table D-2 in Appendix D. They are substantially the same for adults and children. The most frequent were as follows:

- To improve the HbA_{1c} level and prevent long-term complications;
- To reduce hypoglycemia;
- To control hyperglycemia;
- To control wide glycemic fluctuations;
- To have a better quality of life;
- To have greater flexibility in terms of schedule, diet and sports.

The other benefits mentioned on occasion were fewer infections, less stress for the other family members, an improvement in the couple's life, the fact that the pump is less inhibiting in public, in restaurants and on airplanes, the fact that it avoids stains on clothing due to taking insulin by injection, the decrease in the use of health-care services, and the savings that society can achieve by preventing long-term complications.

The following comments illustrate these aspects:

– *Living life like someone who doesn't have diabetes. My HbA_{1c} went from 9.71 to 7.2% in three years, with no complications.*

– *Towards the end, before starting intensive therapy with the pump, I would go to the emergency room once or twice a week with severe hypoglycemia.*

– *It's the complexity of the problems associated with glycemic control that justifies the need to use the insulin pump... [these problems] making daily life impossible for me: [I lived] in fear of falling into a diabetic coma, with no one around at that very moment to help me.*

– *I was on about 10 to 12 injections daily. It was getting to be too much and time-*

15. Sixty percent of the adults had been using the pump for more than one year compared to 30% of the children (according to their parents).
16. The complete report of the results of the survey has been published in a separate document available on request.

consuming. It began interfering with my work and my life. It was like having a second full-time job.

– After 28 years of suffering, I can now enjoy a rewarding life. I got an insulin pump, and I reap its benefits every day. [...] Now, I'm living and no longer just surviving.

Some of the specific benefits of the pump for children are:

- More accurate insulin dosing, which is very important in young children;
- Easier to control the blood glucose level during minor infections, with a number of parents reporting a decrease in the number of hospital stays;
- Improved quality of life, not only for children, but for the entire family;
- Greater autonomy for the child with respect to him/her managing the disease.

– Our lives changed when our son was diagnosed with diabetes but changed just as much on the day he got his pump! His blood glucose levels improved a lot. His nights are stable, with much less agitation. To say nothing of our quality of life. We are now living a near-normal life.

6.1.2 Limitations

The main limitations mentioned are the cost of the pump and supplies, and the high number of daily blood glucose measurements. In children, constant monitoring of the device, because of the risk of ketoacidosis, and changing the cannula were the other main drawbacks mentioned. A number of drawbacks were mentioned on occasion: being attached to a machine 24 hours a day, seven days a week, the fact that the pump is not waterproof during aquatic activities, the aesthetics, and the skin irritation caused by the adhesive dressings.

The following comments illustrate these drawbacks:

– For me, having to perform a lot of capillary blood glucose measurements every day (six to ten) is the main disadvantage, especially because of my occupation.

– Fifty percent more work for the parents. We have to count each gram of carbohydrates that she consumes. We have to do two or sometimes three blood glucose measurements during the night. The cost is astronomical, even with insurance, which causes additional stress.

6.2 INFORMATION, TRAINING AND SUPPORT

Most of the adult patients had obtained information on the insulin pump from their endocrinologist (52%) and the Internet (35%), while the parents of diabetic children indicated that their primary source of information was a support group (45%) or the care team (36%).

The questionnaire looked at the amount of time the various health professionals devote to training patients and starting up pump therapy. Since the answers are subject to interpretation by the patients, they are provided only as an indication. They are summarized in Table 8.

It should be pointed out that there is very wide variation in the amount of time physicians devote to patient training. Furthermore, only 15% of the patients indicated that they had had a consultation with a dietitian when they adopted the insulin pump. This figure seems very low, given the importance of nutrition in managing diabetes. None of the patients indicated that they had met with a pharmacist.

As a general rule, the survey's participants find that there are not enough resources to answer their questions, citing, among other things, the lack of training on the pump on the part of most physicians and the lack of documentation in French. A number of the participants indicated that it is important that the care team do close daily monitoring when treatment is initiated. Some of the participants mentioned the support provided by pump manufacturers, and most of them mentioned the help they had received from the support group that referred them to us.

TABLE 8

Type and duration of patient training

PROFESSIONALS	TIME (HOURS) DEVOTED TO:	
	ADULTS	CHILDREN
Physician	11*	20.0†
Nurse	12	14.5
Company representative	9‡	4.5
Private nurse	-	2.5
Dietitian	3	1.0

* 7 hours together with a nurse
† 14.5 hours together with a nurse
‡ 4.5 hours together with a physician

6.3 INCIDENTS

Two-thirds of the participants mentioned minor incidents with the pump, several of which were due to it not being waterproof. One ketoacidotic episode was reported. Others mentioned problems with the companies not honoring their warranties. A few of the participants indicated that one manufacturer had initiated recalls of defective pumps.

6.4 CONCLUSION

From all the responses, it emerges that people who are presently using an insulin pump derive from it benefits that they consider substantial. All of them agree that the pump has a major impact on their daily life with diabetes, as it enables them to maintain acceptable blood glucose levels and to thus prevent complications, and improves their quality of life and well-being. However, a number of characteristics differentiate the pump users who participated in our survey from most type 1 diabetics, as Colquitt et al. [2002] also observed in their patient survey:

- These patients had come to use the pump after experiencing considerable difficulty controlling their diabetes (severity bias). They were therefore more likely to benefit from the pump than the typical diabetic patient.
- They were more motivated than average, and some of them were highly organized; and
- They were using the pump successfully and were generally enthusiastic about the technology.

These characteristics may prove useful in selecting potential candidates for insulin pump therapy.

7 THE HEALTH PROFESSIONAL PERSPECTIVE

This section explores the opinions of health professionals who have experience with the insulin pump and who were referred to us by *Diabète Québec*. Professionals from four adults care settings (*Hôtel-Dieu de Montréal*, Royal Victoria Hospital, Jewish General Hospital and *Hôpital Maisonneuve-Rosemont*) and three pediatric care settings (*Hôpital Sainte-Justine*, Montreal Children's Hospital and *Centre hospitalier de l'Université Laval*) were interviewed. For the most part, they were 1- to 2-hour interviews with members of the multidisciplinary team. In two cases, the interview was conducted by telephone. It concerned the health professionals' opinions regarding the safety and efficacy of the pump compared to multiple injections. Current practice, patient selection criteria, service organization problems, and training of the health professionals concerned were also explored. The interview guide is presented in Appendix E.

7.1 SAFETY AND EFFICACY

All the health professionals agree that the current pumps are safe, if the patient is conscientious, serious, motivated and disciplined, and has received complete training. They are "infinitely" safer than they were 20 years ago. A number of the professionals pointed out that it is a machine and that any machine can malfunction.

For adults, opinions are divided as to the comparative efficacy of the pump in terms of glycemic control. A number of the professionals referred to the scientific literature, which does not find the pump to have a very high degree of efficacy compared to multiple injections. All of the professionals in question say that the pump is effective in carefully selected patients and that it is a cost-effective tool for a minority of adult patients. The opinions of Québec health professionals concur with Colquitt and colleagues' conclusions [2002].

– *In theory, the pump may be scarcely better than multiple injections, but, based on our experience, it's comparable in everyday life, except in very rare cases, but the difference is not clinically significant.*

One nurse said the following:

– *For people who really need it, it's a question of survival, not just of quality of life.*

In pediatrics, clinical opinions are more categorical. All the clinicians interviewed are convinced that the pump is permitting better glycemic control in the children to whom they have prescribed it. Glycemic excursions are less pronounced and easier to correct, and the pump reduces morning hyperglycemia, permits better treatment adjustments during "minor illnesses", such as gastroenteritis, avoids emergency room visits and hospitalizations, and improves the patient's quality of life. They point out that pump installation and monitoring are more difficult with pediatric patients, that the parents have to have a good understanding of the impact of diabetes on the body, and that education is essential. They therefore conclude that the pump is not for everyone, but only for selected candidates.

7.2 CURRENT PRACTICE

7.2.1 Patient selection

The patient selection criteria mentioned by the health professionals who were interviewed are presented in Table E-1 in Appendix E. Coverage by private insurance is presently the main criterion in Québec. The percentage of patients and the clienteles that would benefit from pump therapy, even if there were no financial obstacles, vary enormously according to these professionals' practice setting and clientele. In adult care settings, some see the pump providing benefit only in very rare

cases, others in 5%, 20% or even 50% of their clientele. In pediatric care settings, professionals estimated that 30 to 75% of patients would benefit from the pump. In Canada, a study conducted at a Toronto pediatric clinic found that 15% of its diabetic patients are treated with the pump [Liberatore et al., 2004].

Many professionals consulted pointed out that a number of patients encouraged to try the pump to resolve certain difficulties with glycemic control turn down this treatment modality when they are told how it is used and what it involves. In addition, some patients who hear that the pump is a miracle tool reverse their decision to use it when they are properly informed of what this treatment requires. This is reported in the scientific literature as well, as a certain percentage of the subjects in randomized trials who had been randomized to the pump refused to adopt it [Cohen et al., 2003a; DeVries et al., 2002] or chose to discontinue pump therapy after the study ended [Weintrob et al., 2003].

7.2.2 Training and follow-up of patients on pump therapy

All the care settings emphasize the crucial role of diet and point out the shortage of dietitians.

7.2.2.1 Patient education

Each care setting has its own way of doing things. A physician and a nurse are generally involved in training, together with a dietitian, at some locations. Group education seldom works for more than two patients at a time. The companies' role in education prior to pump use varies, and some wonder if it is ethical to leave education to the companies with no quality control and what the medical liability is in such cases. All the care settings deplore the complete lack of French-language patient materials.

7.2.2.2 Installation

As a general rule, the pump is installed at an outpatient clinic in the case of adults or at a day hospital in the case of children. In pediatric settings, caregivers emphasize the importance for a social worker and a psychologist to evaluate the family and school situation.

7.2.2.3 Postinstallation follow-up

The resources in terms of physician and nursing time devoted to postinstallation follow-up are important. The follow-up generally requires daily contact between the patient and the care team. Contact gradually diminishes from daily to weekly after four to six weeks. Based on the experience of most of the care settings, in the long run, pump-treated patients become more independent and can adjust doses and boluses on their own. One physician estimates the need for education and nursing support at about two or three days a week for 40 to 60 adult patients.

7.3 ORGANIZING OF SERVICES

Care teams feel that there are organizational problems that need to be corrected before an insulin pump therapy access program can be instituted. One medical specialist feels that "if the government embarks on a pump access program, a framework will be an absolute necessity: start with a trial, have criteria of success—not just the HbA_{1c} level—and evaluate everything. Otherwise, it could become a shameless waste of public funds!" A number of preconditions should be met:

- **Availability of a trained multidisciplinary team.** Given the limited availability of the current resources, health professionals are inclined to propose consolidation at a few centres only: one or two in Montreal, one in Quebec City, one in Hull and one in Sherbrooke. Since education varies enormously from one setting to another, it should be standardized.

- **Patient selection.** All the care settings agree that there should be specific pump prescription and coverage criteria but fear that these clinical criteria are difficult to apply in practice.
- **Very clear pump access modalities**, such as special, limited prescribing, even if this involves more procedures; determining a specific number of pumps to be available per clinical setting in proportion to the patient population; and a trial period for which a pump is loaned.
- **A full range of clinical services.** Presently, the manufacturers have a 24-hour, toll-free line, in English only, for anything that has to do with technical problems. In the case of one company, follow-up service is provided by representatives who cover the entire province of Québec.
- **Fair access in the regions.** For usual diabetes follow-up, patients in the regions should have access to a local endocrinologist or to a diabetes nurse at a local day centre. It is felt by some that this could be difficult to organize. One care setting proposes that traveling teams be set up to guarantee access in the regions.
- **Anticipation of the impact on other activities in the health-care system.** When, in an emergency situation, a patient on pump therapy consults outside his/her usual care setting, this can pose a problem. For children in day-care centres or at schools, it is difficult for CLSCs to provide information to the other individuals who look after the child during the day. This task usually falls to hospital personnel.

7.4 TRAINING OF HEALTH PROFESSIONALS

All the care settings agree that little or no training on the use of the pump is provided to health professionals. Most often, it is a question of self-teaching out of personal interest, and the teaching materials are available in English only. The companies offer half-day training sessions, after which they propose certification. All the nurses with whom we met have taken this training, but all of them are skeptical about the certification: "You can't become an expert in three hours!" In addition, each company has its own particular model of pump, with its particular functions and accessories, with the result that it is rather difficult to keep up to date on all these models, which change on a regular basis. One nurse said, "It would take half a day of training per new model!" All the care settings agree that, if training prior to pump use is to be provided, this could be done only by a person with sufficient practice volume. This individual could thus develop leading-edge expertise and devote the necessary effort and skills to continuing education. Dividing this task among all the members of a care team would run counter to this imperative.

Clinical training on pump therapy for physicians is provided only at specialized centres. A number of these settings have an on-call system in endocrinology, where all the physicians know how to correct insulin dose adjustment problems with the pump, thanks to a protocol for converting from multiple injections to basal levels in continuous infusion therapy.

8 ECONOMIC ASPECTS

8.1 REVIEW OF THE SCIENTIFIC LITERATURE ON THE COST-EFFECTIVENESS OF PUMP THERAPY

In their report, which served as a source of information for the National Institute for Clinical Excellence (NICE) guidelines [2003], Colquitt et al. [2002] examined the available data on the cost-effectiveness of pump therapy compared to that of multiple insulin injections and did not find any publications on this topic. According to them, the economic models concerning type 1 diabetes compare conventional therapy and intensive therapy and therefore do not provide any useful information for determining the cost-effectiveness of pump therapy in relation to multiple insulin injections. Nonetheless, a number of groups propose models to assist in clinical or financial decision making [Palmer et al., 2004].

8.1.1 Recent publications

Four economic studies comparing insulin pump therapy and multiple injections with NPH were identified, including one published in a scientific journal [Scuffham and Carr, 2003], two in the form of abstracts [Roze et al., 2002; Roze and Palmer, 2002], and one as a paper presented at a health economists conference [De Sola-Morales et al., 2004]. The characteristics of these studies and their main findings are presented in Table F-1 in Appendix F.

The 8-year Markov model that Scuffham and Carr [2003] constructed to compare the costs and utility of these two treatment modalities took hypoglycemic and ketoacidotic episodes into account. The model showed the incremental cost per QALY (Δcost/ΔQALY) with the pump was £11,461 (CA$27,736[17]) (standard deviation: £3,656 [CA$8,848])[18]. The authors state that pump therapy would be a cost-effective investment if targetted at those patients who can benefit from it the most, i.e., those who experience more than two severe hypoglycemic episodes per year and who have to be hospitalized at least once a year because of these hypoglycemias. However, they feel that a high rate of hypoglycemic episodes is not a sufficient criterion for justifying insulin pump therapy. The patient must be able and motivated to manage this type of treatment, and the risk of discontinuation should be low. To reduce this risk, Sanfield et al. [2002] recommend targetting individuals who are likely to benefit from pump therapy and propose a screening protocol for this purpose. They feel that it would be more cost-effective to institute a structured education program for patients who self-administer multiple insulin injections and to reserve the pump solely for those who continue to experience severe hypoglycemic episodes.

Roze et al. [2002], who consider all the potential complications of diabetes in their modelling techniques applied over a 50-year period, conclude that the additional cost per life-year gained (€1,348, CA$2,198) is within acceptable limits[19]. The abstract is not, however, clear enough for us to assess the robustness of the methodological underpinnings of this model. The abstract of another economic study, by Roze and Palmer [2002], indicates that the additional costs generated by pump therapy are covered only in part by the savings achieved as a result of the reduction in treatments for renal failure.

The Catalonian health technology assessment agency, the *Agència d'Avaluació de Tecnologia i Recerca Mèdiques* (AATRM), will soon be publishing its own cost-utility analysis. Preliminary results were, however, recently presented at a conference for health econo-

17 Annual Bank of Canada exchange rates were used to express the costs in 2004 Canadian dollars (January 1, 2004 to September 30, 2004). Thus, US$1 = CA$1.33, €1 = CA$1.63, £1 = CA$2.42.

18 Depending on the willingness-to-pay threshold (£12,000 [CA$29,040] to £15,000 [CA$36,300]), 70 to 80% of cases might be acceptable.

19 The authors do not provide any figures on what they mean by acceptable limits.

mists[20]. The agency has determined the incremental cost per QALY to be €288,117 (CA$469,631), or well above the theoretical willingness-to-pay threshold of €30,000 (CA$48,900) per QALY [De Sola-Morales et al., 2004]. In light of these results, the authors suggest that the pump be reserved exclusively for patients who fail to achieve glycemic control with multiple injections. Lastly, Bolli et al. [2004], in an abstract of a study that compared pump therapy and multiple injections with glargine, estimate that pump therapy is four times more expensive for an equal therapeutic effect and that therapy by multiple injections with glargine is more cost-effective for type 1 diabetics. Since the methodological details of the economic analysis are not provided, we will have to wait until the study is published in order to assess the basis and soundness of this conclusion.

8.2 COST DIFFERENTIAL WITH PUMP THERAPY

A cost analysis approach was used to determine the cost of insulin pump therapy compared to intensive therapy with multiple injections (the cost differentials details for pump therapy are provided in Tables G-1, G-2 and G-3 in Appendix G). Cost differentials were estimated in accordance with the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) guidelines. However, these estimates are limited to the direct costs generated by the four main components of pump therapy, namely, the purchase of an insulin pump, the accessories (reservoir or cartridge, infusion set, batteries), the training of users (children and adults), and supplies (lancets and blood glucose monitor test strips, ketone strips, adhesive dressings and antiseptic swabs).

When comparing the two treatment modalities, we did not estimate the benefits resulting from avoided complications, since, according to Scuffham and Carr [2003], it is difficult to determine which intensive treatment modality is more effective. The cost of insulin was not taken into account either, given that it is difficult to obtain accurate data on insulin consumption in type 1 diabetics on pump therapy (children and adults). This decision is also based on the facts that the unit cost of insulin is low [Leichter, 2003] and that Colquitt and colleagues' report [2002] indicates that pump therapy could lead to a small reduction in insulin doses.

The cost differentials are estimated from a health-care system perspective, where certain cost components of pump therapy may be covered by the public system or the private sector. Presently, in Québec, insulin pumps are only partially covered by certain private organizations, while supplies, such as insulin, blood glucose monitor test strips and ketone strips, are generally covered by the public system. In Canada, only the Northwest Territories, Nunavut and the Yukon cover insulin pumps and supplies for all diabetics (type 1 and type 2). Only supplies are fully or partially covered in Nova Scotia (on a case-by-case basis), New Brunswick, Manitoba, Saskatchewan, Alberta, British Columbia (based on net family income) and Prince Edward Island [CDA and Diabète Québec, 2003]. In Ontario, a bill that would grant coverage for the pump is presently in second reading in the legislative assembly (Bill 55). However, its adoption is not imminent[21]. Colquitt and colleagues' report [2002] includes a list of all the countries in which the pump is covered and an estimate of the number of pumps in circulation provided by INPUT, a British advocacy group that promotes the use of the pump.

8.2.1 Cost analysis method

The cost estimates for pump therapy are not derived from observing the use of services by groups of diabetics, but come from various validated information sources (see Section 8.2.2). Although the average lifespan of a pump is estimated at eight years[22], it is generally recognized that that pumps are replaced every five years and that training is required

20. 14th Health Economics Conference, France, May 2004.

21. Dr. Leslie Levin, Head, Medical Advisory Secretariat, Ontario Ministry of Health and Long-term Care, personal communication, 2004.

22. According to industry data, the average lifespan of an insulin pump is eight years, but the warranty only covers the first four years of use, which means purchasing a new pump every five years.

each time. We thus considered that the purchase or replacement cost of a pump and the cost of training are incurred every five years, whereas the cost of the accessories and supplies is incurred every year.

The equivalent annual cost differentials (EACDs) per insulin pump user were estimated, with the major investments—the pump and training—spread out over several years and these cost differentials reflecting the opportunity cost that these investments involve. The EACD expresses here the annual value of the additional resources used by a diabetic who opts for treatment with the insulin pump (Table 9). An estimate of the potential number of users in Québec was made on the basis of the prevalence rates of type 1 diabetes (existing cases) in affected adults and children and on the implementation rates of this technology as provided by existing data or reimbursement guides from other countries (Tables 10 and 11). Various scenarios were thus developed to determine the disbursements required every five years for the purchase or replacement of an insulin pump and for training the cohort of prevalent cases (Table 10). Using these parameters, we determined the annual cost differential for a reimbursement program for type 1 diabetics who are presently theoretically eligible for pump therapy (Table 11). This cost figure does not, therefore, include new patients who may be treated with the pump in the future, since there are no reliable data on the incidence of type 1 diabetes in Québec.

Most of the cost estimates are based on market prices expressed in 2004 Canadian dollars. The cost of insulin pumps is an arithmetic mean of the costs of the four main models sold in North America, and the cost estimate for the accessories and supplies reflects the recommendations of the manufacturers, industry representatives and a diabetes nurse regarding the frequency at which each item should be replaced[23]. Blood glucose monitor lancets and test strips are used at a substantially higher frequency than that recommended for multiple injection therapy, especially during the first three weeks of pump therapy, when the user has to prick him/herself 12 times a day to determine his/her blood glucose profile[24]. On the other hand, fewer antiseptic swabs are used with pump therapy (one every three days, compared to four per day with multiple injections). As for the adhesive dressings used to keep the cannula in place, it will be noted that the cost estimates in this report do not reflect the additional costs incurred by using hypoallergenic dressings, such as Tegaderm™ (see the last note under Table G-3 in Appendix G).

Lastly, the cost estimate for training was derived from a realistic scenario based on the opinions of clinicians who provide training to diabetics and on interviews with diabetic patients on pump therapy (see Table G-2 in Appendix G). It will be noted that the cost of training professionals who provide patient education could not be estimated, since there are no data on this subject. We do, however, know that this cost is directly associated with the frequency with which new insulin pumps are placed on the market, the number of patients to be trained, the number of professionals on the care team and the number of teams available in a given area.

8.2.2 Sources of information

The cost of insulin pumps was determined from promotional materials and price lists from the main pump manufacturers in North America (Medtronic/Minimed, Animas and Deltec Cozmo), as was the cost of the accessories and supplies. Telephone interviews with a nurse (affiliated with the Royal Victoria Hospital, part of the McGill University Health Centre) who specializes in diabetes education and the use of insulin pumps, and interviews with pharmacists in the Montreal area were conducted to validate all the estimates that had been made. The results of a questionnaire administered in December 2003 to parents of children on pump therapy and to adults on pump therapy were also used to estimate the cost of the training required for effective pump use. The number of professionals in-

23. The reservoir and tubing should be changed every six days so that the insulin does not crystallize, the cannula every three days in order to reduce the risk of infection, and the batteries according to their respective mean lifespan (three to eight weeks).

24. After the first three weeks, a pump user has to prick him/herself six times a day, compared to four times a day with multiple injections.

volved in training pump users and the amount of time that they devote to various activities were obtained from telephone interviews with the diabetes nurse. The hourly rates for professionals involved in this type of training were determined from the official recognized sources[25].

8.2.3 Results

Table 9 shows the equivalent annual cost differential (EACD) for each of the main treatment components for an insulin pump user. It also shows the frequency at which the cost of these components is incurred. Based on these results, the use of pump therapy in a Québec context costs CA$4,756 a year more than multiple injection therapy. This cost differential is incurred for as long as the patient uses the pump.

Specifically, the average cost of an insulin pump is CA$6,063, with the accessories costing CA$2,384 annually (Table G-1, Appendix G). The time devoted to training and following pump users costs, on average, CA$2,332 per user, adults and children combined. The meetings with the care team, which consists of a medical specialist, a nurse and a dietitian, contributes to this cost, but the main contributing factor is the nursing time devoted to training children and their parents (Table G-2, Appendix G). Retraining is required whenever a user purchases a new pump or when his/her pump has to be upgraded. The mean cost differential of the supplies used in the context of insulin pump therapy is CA$487 at the start of treatment, then CA$347 for each subsequent year. In actual fact, these costs could be much higher if the pump user would use a product like Tegaderm™ and if the costs thus incurred were eligible for reimbursement under the public plan, which is presently not the case[26]. In such case, the annual mean cost of adhesive dressings would increase from CA$58 to CA$470 per user (Table G-3, Appendix G). According to information obtained during telephone interviews with a diabetes nurse, about 50% of pump users presently use this type of product.

8.3 POSSIBLE IMPLEMENTATION SCENARIOS

It is estimated that there are presently about 28,000 adults and between 2,000 and 2,500 children with type 1 diabetes in Québec. Estimating the actual number of type 1 diabetics in Québec is technically problematic because the available databases do not distinguish between type 1 and type 2 diabetes. The *Institut national de santé publique du Québec* (INSPQ) is presently taking steps to refine the methods it uses to estimate the prevalence and incidence of type 1 diabetes, both in adults[27] and children. In the United Kingdom, using Colquitt and colleagues' systematic review [2002] and data from the group Pump Management for Professionals (PUMP), NICE [2003] set the initial reimbursement scenarios at 1 and 2%. As well, one scenario involving a 5% implementation rate was put forth by French professionals. These scenarios are detailed in Tables 10 and 11. Table 10 shows the disbursements incurred every five years for purchasing or replacing insulin pumps and training the cohort of prevalent cases for the three possible scenarios, that is, an implementation rate of 1 and 2% [NICE, 2003] and of 5% (estimated level of use in France). Table 11 presents the annual costs of covering insulin pump therapy in an established program, according to these various scenarios, for the same cohort of prevalent cases.

25. Telephone interview with a *Fédération des infirmières et infirmiers du Québec* (FIIQ) official, 2003; consultation of the document titled "*CSN, Convention collective – nomenclature des titres d'emploi, des libellés et des échelles de salaires des syndicats affiliés à la Confédération des syndicats nationaux (CSN); Fédération de santé et services sociaux – CSN (FSSS-CSN) and Fédération des professionnels – CSN (SP-CSN), 2000-2002*"; consultation of the Web sites of the *Conseil du trésor* (2003) and *Emploi Québec* (2004).

26. Coverage may, on an exceptional basis, be granted to patients who manage to obtain "exception patient" status after taking legal steps to this end.

27. Marie Émond, research officer, INSPQ, personal communication, November 2004.

TABLE 9

Equivalent annual cost differential (EACD) for an insulin pump user compared to multiple injection therapy*

DATA USED TO CALCULATE THE EACD	FREQUENCY	EACD†
Description (mean cost in CA $)		
Insulin pump ($6,063)	Every 5 years	$1,400
Accessories (reservoir or cartridge, infusion set, batteries) ($2,384)	Every year	$2,384
Training (adults: 12 hours; children: 20 hours) ($2,332)	Every 5 years	$539
Insulin (–)	Variables	Variable
Supplies (blood glucose monitor lancets and test strips, ketone test strips, dressings and antiseptic swabs)‡ ($487)§	Every year	$433
Estimated total EACD		$4,756

* In 2004 Canadian dollars, based on the price of the four main models of pump.
† Annual cost calculated for a 5-year period, using a discount factor of 0.05 (4.3295) [Drummond et al., 1997, Table 2, p. 94].
‡ The breakdown of the cost of supplies is given in Table G-3 in Appendix G.
§ The cost is $347 for each subsequent year, since fewer blood glucose monitor lancets and test strips are used than at the start of treatment.

TABLE 10

Disbursements incurred every five years for purchasing or replacing insulin pumps and for training the cohort of prevalent cases according to various scenarios

CATEGORY OF PATIENTS	TOTAL NUMBER OF TYPE 1 DIABETICS	TARGET NUMBER OF DIABETICS			TOTAL COST* FOR THE COHORT (IN MILLIONS OF CA $)		
		IMPLEMENTATION SCENARIOS					
		1%†	2%†	5%‡	1%†	2%†	5%‡
Adults	28,000	280	560	1,400	2.4	4.7	11.8
Children	2,000	20	40	100	0.2	0.3	0.8
Total	**30,000**	**300**	**600**	**1,500**	**2.6**	**5.0**	**12.6**

* Based on a cost of $8,395 (pump and training).
† NICE, 2003.
‡ Based on the estimated use in France, 18th World Diabetes Conference.

TABLE 11

Annual cost differential for the coverage of insulin pump therapy in an established program according to various scenarios (cohort of prevalent cases)

CATEGORY OF PATIENTS	TOTAL NUMBER OF TYPE 1 DIABETICS	TARGET NUMBER OF DIABETICS			TOTAL ANNUAL COST* (IN MILLIONS OF CA $)		
		IMPLEMENTATION SCENARIOS					
		1%†	2%†	5%‡	1%†	2%†	5%‡
Adults	28,000	280	560	1,400	1.3	2.7	6.6
Children	2,000	20	40	100	0.1	0.2	0.5
Total	**30,000**	**300**	**600**	**1,500**	**1.4**	**2.9**	**7.1**

* Based on the EACD, estimated at CA$4,756.
† NICE, 2003.
‡ Based on the estimated use in France, 18th World Diabetes Conference.

The disbursements incurred every five years for purchasing or replacing pumps and for training would thus vary from CA$2.6 million to $12.6 million (as at 2004). If all the costs of pump therapy are taken into consideration, including the recurrent cost of the accessories and supplies in an established program, the annual cost differential would be between CA$1.4 and $7.1 million, depending on the scenario. These costs would be incurred for the entire period equal to the mean life expectancy of the diabetics on pump therapy. These costs are underestimated, since they do not take into account the new users who might adopt pump technology over the years. One pump manufacturer estimates that there are presently 500 pump users in Québec[28], which works out to an implementation rate of close to 2%. Based on this estimate, the disbursements incurred for purchasing or replacing pumps and for training would be CA$5 million, and the annual cost differential for pump therapy coverage would be approximately CA$2.9 million.

Offering the insulin pump to all eligible prevalent cases is an option that involves a large disbursement at startup, and this disbursement would be made every five years. This specific effect would diminish as new patients become eligible for pump therapy each year, although this would not prevent the total cost of coverage from gradually increasing.

28. R. Paquin, MedTronics, personal communication, December 2003.

9 DISCUSSION

A review of the scientific literature indicates that studies of insulin pump therapy use multiple injections with NPH or glargine as the comparator treatment. It will be noted that insulin glargine only recently made its appearance on the international market and is still not commercially available in Canada. NICE [2003] recommends the insulin pump solely for patients who have failed to effectively control their blood glucose level after six months of treatment with multiple injections of glargine. It does, however, state that these recommendations should be reassessed after the publication of randomized, controlled trials of insulin pump therapy with multiple injections of glargine as the comparator treatment. These recommendations are based on the available data from studies involving adult diabetics. Despite the absence of pediatric studies on this subject, NICE also suggests applying these recommendations to children. This assessment takes into account the new studies published since the report that Colquitt et al. [2002] prepared for NICE.

9.1 SAFETY

As regards the frequency of severe hypoglycemic episodes, the conclusions of the recent studies comparing pump therapy and multiple injections with NPH for adults and children that were identified in connection with this report concur with the conclusions of Colquitt and colleagues' report [2002]. Randomized, controlled trials show no significant difference, either in children or adults, in terms of the incidence of severe hypoglycemic episodes between the two treatment modalities. Nonrandomized studies do, however, report fewer severe hypoglycemic episodes in pump-treated patients, which could be explained by patient selection in this type of study, where pump therapy is offered to those patients who are most likely to benefit from it.

Two nonrandomized studies, one involving adults selected at the beginning of the study [Lepore et al., 2004], the other involving children [Alemzadeh et al. 2004], found that pump therapy and multiple injections with glargine were more effective than multiple injections with NPH in reducing the incidence of severe hypoglycemic episodes.

As for the incidence of ketoacidotic episodes, no significant difference between pump therapy and therapy by multiple injections with NPH has been found. However, older studies tended to find more ketoacidotic episodes with pump use. As for the more recent randomized, controlled trials, the sample size was too small to draw any conclusions, whether for adults or children. Nonetheless, most studies have found a higher absolute number of ketoacidotic episodes with the pump than with multiple injections.

There are other complications associated with the use of the insulin pump, but they are minor. There is a risk of pump malfunction, but the extent of the potential impact of these malfunctions on a patient's health cannot be assessed from the current scientific literature. To protect themselves against potential malfunctions, pump users need to perform daily blood glucose measurements more frequently than patients treated with multiple injections.

9.2 EFFICACY

9.2.1 Adults

According to the scientific literature, for typical, randomly selected adult diabetics, pump therapy probably improves the HbA_{1c} level more than multiple injections with NPH. This improvement is, however, modest (mean decrease of 0.51 to 0.6%). Just one new study has shown a significant effect in a subgroup of patients (with specific criteria, including an HbA_{1c} level $\geq 8.5\%$) selected because they had

had long-standing problems with glycemic control. In such cases, the pump might prove more beneficial than treatment by multiple injections with NPH (mean decrease of 0.84% in the HbA_{1c} level) [DeVries et al., 2002]. The impact of this improvement on the incidence of long-term complications cannot, however, be assessed from the currently available data, especially in light of the recent studies [EDIC Research Group, 2003; Service and O'Brien, 2001], which indicate an HbA_{1c} cutoff of 8.5% and a mean blood glucose level of 8.3 mmol/L as predictive factors for the progression of nephropathy and retinopathy, respectively. Various cost-effectiveness modelling scenarios were found in the literature, but because of the limitations of these studies, no conclusions can be drawn as to the long-term cost-effectiveness of insulin pump therapy. The randomized and nonrandomized studies that have compared the pump and multiple injections with glargine indicate that pump therapy does not lead to a significant improvement in HbA_{1c} levels. One recent study estimates the cost of pump therapy to be four times higher than that of multiple injections with glargine and concludes that insulin glargine is more cost-effective than the pump in an unselected population of diabetics [Bolli et al., 2004].

Compared to multiple injections with NPH, the pump may offer certain advantages in terms of glycemic control and quality of life, particularly to groups with inadequate glycemic control at the outset (HbA_{1c} level $\geq 8.5\%$). In adults, the effect of insulin pump therapy on glycemic control is, however, comparable to that of treatment by multiple injections with glargine. Assuming an equal therapeutic effect, insulin pump therapy is much more expensive than multiple injections with glargine. It therefore seems that treatment by multiple injections with glargine will be the preferred treatment when this insulin becomes commercially available in Canada. However, according to patients and clinicians, there will still be individuals who will not be successful in adequately controlling their diabetes, even if they use insulin glargine. Pump therapy might thus be one therapeutic option to consider for such patients.

9.2.2 Children

For the vast majority of children, the insulin pump is not more effective than multiple injections with NPH. The pump might improve their glycemic control, but this improvement is modest. For certain selected groups, the extent of the improvement in the HbA_{1c} level could not be quantified by a meta-analysis, but the nonrandomized studies involving various selected populations situate it between 0.46 and 1.5%. It is difficult to assess the impact of this improvement on the incidence of long-term complications. This conclusion is the same as for adults.

The results of a first randomized, controlled pediatric trial [Doyle et al., 2004] indicate that pump therapy permits better glycemic control than multiple injections with glargine. Multiple injections with glargine are, however, reportedly no more effective than multiple injections with NPH as regards glycemic control. The large number of injections that treatment with glargine requires—since it cannot be mixed with other insulins for injection—has an impact on compliance to injection schedules in youths and, as a result, on their glycemic control.

In light of this information, the clinical significance of the results of the study by Doyle et al., according to whom the pump is superior to multiple injections with glargine as regards glycemic control but has a comparable impact on the incidence of severe hypoglycemic episodes, is questionable. In order to make pediatric recommendations, one would need to examine the benefits specific to pump therapy and to therapy by multiple injections with glargine and compare them with the results of numerous studies which indicate that the therapeutic effect of the pump and that of multiple injections with NPH are identical. It will be noted that treatment with insulin glargine is one option for diabetic youths who have a problem with severe hypoglycemic episodes. In the case of diabetic children with inadequate glycemic control, no specific criteria for selecting those who would truly benefit from pump therapy can be established from the scientific literature. The age groups and the

selection criteria for the populations studied in the literature vary enormously, and management of the disease differs considerably between preschoolers and adolescents [DiMeglio et al., 2004a]. The pediatric health professionals consulted estimate that between 30 and 75% of their patients would benefit from the pump. These figures largely exceed those used for the implementation scenarios presented in this report.

The results of studies on the improvement in the quality of life of pump users are contrary to what was indicated by the patients who responded to our survey, since they experienced specific problems adequately managing their diabetes before using the pump.

Based on the available data, insulin pump therapy for children is no more effective than multiple injections with NPH, except, perhaps, for certain selected groups. The effect of insulin glargine on glycemic control is difficult to assess in children, and the benefits that it confers to adults and children differ, with the exception, perhaps, of its effect on the incidence of severe hypoglycemic episodes. Based on the available data, the treatment to be preferred for the general population of diabetic youths is multiple injections with NPH. However, for selected patients, the increased flexibility offered by pump therapy might improve glycemic control and the quality of family life.

9.3 PATIENT SELECTION

According to the literature consulted, insulin pump therapy is effective and entails no greater risks than multiple injection therapy, if precautions are taken. The advantage of pump therapy for selected patients was confirmed by the teams of health professionals that were interviewed for the purposes of this report. Similarly, the survey conducted among pump-treated diabetics found that many of them experience hypoglycemic and hyperglycemic episodes, and that the pump reduces their symptoms and improves their quality of life. On the other hand, for both adults and children, the efficacy gain is obvious only for patients who meet specific criteria. Most of the selection criteria mentioned by the specialists who were consulted for the purposes of this report coincide with those mentioned in the studies involving adult diabetics. As for selecting children, we cannot, on the basis of the scientific literature, propose any uniform criteria. The paucity of evidence in favour of pump therapy as a general treatment option is inconsistent with the opinions of the health professionals who were interviewed, as they are rather in favour of pump therapy for children. The group of parents of diabetic children consulted is also much in favour of pump therapy and is lobbying for access to this technology. The arrival of insulin glargine on the Canadian market should make multiple injection therapy even more attractive for adults. As for the comparative efficacy of this treatment modality in children, we will have to await the results of future studies on this topic before we can draw any conclusions.

9.4 ECONOMIC CONSIDERATIONS

Schuffman and Carr [2003] present criteria for selecting patients who are most likely to benefit from insulin pump technology. In particular, they mention adults who experience at least two severe hypoglycemic episodes a year and who require admission to hospital at least once a year. In their economic study, De Sola-Morales et al. [2004] determine the incremental cost per QALY with pump therapy to be CA$469,631, which is well above the theoretical willingness-to-pay threshold of CA$48,900 per QALY. Presently, in Québec, the proportion of pump-treated diabetics is about 2%. Implementation cost scenarios for Québec have been developed, based on the theoretical percentage of patients who might benefit from this technology. The difficulty in targetting, by means of specific criteria, the percentage of patients who would benefit from pump therapy is the main limiting factor in the implementation scenarios.

Intensive therapy is recognized as offering a definite advantage over conventional therapy with regard to glycemic control (expressed as the HbA_{1c} level) and with regard to delaying the onset of certain diabetic complications. According to the health professionals who were interviewed, a good number of adult diabetics in Québec are receiving conventional therapy. The main reasons put forth by these professionals to explain this situation are that the patients and clinicians are pleased with the outcomes of conventional therapy or that the current resources are inadequate to provide the necessary ongoing training and follow-up to patients who might benefit from intensive therapy. At a time of budget constraints, such as those experienced by the current system, a number of these professionals wonder if it would be appropriate to invest in the additional resources required for intensive therapy by insulin pump for a limited group of patients instead of investing to provide broader access to intensive therapy with multiple injections to all type 1 diabetics.

10 CONCLUSION

Multiple injections with NPH are presently the treatment recommended in the Canadian guidelines for the treatment of diabetes [CDA and Diabète Québec, 2003], and this treatment is available in Québec. For the general population of adult diabetics, the pump may offer a modest advantage in terms of glycemic control (mean decrease in the HbA_{1c} level of 0.51%) in relation to multiple injection therapy with NPH, with no apparent additional risks. For the general population of diabetic children, the pump does not appear to be more beneficial than multiple injections with NPH.

For adult patients selected because of inadequate glycemic control (HbA_{1c} level $\geq$ 8.5%), one randomized, controlled trial reports a greater improvement (mean decrease in the HbA_{1c} level of 0.84%). The case series involving selected children report a greater improvement with the pump as well, although it cannot be quantified. The evidence concerning the effect of the modest-at-best improvement that pump use might offer in terms of preventing long-term complications and in terms of quality of life are not sufficient to give an informed opinion of the cost-effectiveness of the insulin pump for target populations.

The authors cite various criteria for selecting adult patients who are likely to benefit from the pump, but these expert opinions are not evidence-based.

For the general population of adult diabetics, the pump's efficacy is comparable to that of multiple injections with glargine. Since the pump costs much more, and since insulin glargine might soon be commercially available in Québec, there is less interest in pump therapy for adult diabetics. Nonetheless, for some patients who may not be able to achieve adequate glycemic control with multiple injections with glargine, the pump may be a cost-effective option. Moreover, NICE considers patients with major problems with hypoglycemia or nocturnal glycemic control (dawn phenomenon) as a priority group for research comparing multiple injections with glargine and the pump [NICE, 2003]. For children, since the potential effect of insulin glargine on glycemic control seems to be less promising than for adults, multiple injection therapy with NPH remains therefore the first choice.

11 RECOMMENDATIONS

AETMIS recommends that:

1) as set out in the Canadian practice guidelines, the preferred therapeutic approach to type 1 diabetes, in both adults and children, be based on intensive therapy with multiple daily insulin injections;

2) therapy by continuous subcutaneous insulin infusion (insulin pump) be recognized in Québec as a treatment modality that might be indicated for a limited, selected group of type 1 diabetics (various selection criteria based on expert opinions are cited in this report);

3) the *Ministère* consider setting up a multidisciplinary task force (including *Diabète Québec*, and the clinical and research communities) charged with:

- identifying consensus criteria for patient selection and for prescribing and monitoring insulin pump therapy;
- designating clinics that would participate in the implementation of pump therapy and determining the composition and role of the professional team required;
- developing common candidate selection, patient education and follow-up tools;
- monitoring the implementation of pump therapy; and
- reevaluating the use of pump therapy in Québec some time after it is introduced;

4) the consensual criteria for the use of the pump be reviewed periodically in light of the new evidence that becomes available after this report, in particular, from studies comparing the insulin pump and multiple injection therapy with glargine, since glargine may soon be available in Canada (technology watch);

5) a clear, consistent policy governing the use of the insulin pump be developed and made part of a broader initiative for managing diabetes in Québec that would take into account the need to increase the ability of Québec's health-care system to offer intensive therapy to all type 1 diabetics;

6) two options for standardizing the prescription and coverage modalities be examined:

- consider the pump an exceptional treatment modality for exceptional patients, with access granted by the *Régie de l'assurance maladie du Québec* (RAMQ) on a case-by-case basis according to the criteria established by the above-mentioned task force and/or on request by a physician;
- institute systematic pump prescription and utilization auditing and monitoring procedures based on set criteria in collaboration with the clinical settings concerned, possibly by creating a registry of pump-treated patients or developing tools for selecting cases on a priority basis within a predetermined budget allowance;

7) a full range of technical services be provided in French in Québec by the manufacturers and distributors of insulin pumps; and

8) research on patient selection criteria and the cost-effectiveness of insulin pumps in the Québec context be considered an important avenue of investigation by the *Fonds de la recherche en santé du Québec* (FRSQ).

APPENDIX A: STUDIES OF THE INSULIN PUMP

TABLE A-1

Summary of the conclusions and recommendations of two recent health technology assessment reports on the insulin pump

	NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE (NICE) [COLQUITT ET AL., 2002]	AGÈNCIA D'AVALUACIÓ DE TECNOLOGIA I RECERCA MÈDIQUES (AATRM) [PONS, 2000]
Conclusions	The technology has evolved considerably since the publication of a number of the identified studies. Randomized, controlled trials (RCTs) show that the pump provides modest but real benefits. Observational studies report greater benefits, probably because they selected patients who might benefit the most from pump therapy. Pump therapy should probably be limited to a small percentage of diabetics, but the exact percentage is uncertain.	Good glycemic control, but modest improvement compared to multiple injections. Patient motivation and commitment are essential for achieving the desired metabolic and therapeutic benefits. Support from and training by specialized professionals may contribute to success. There is no evidence for establishing patient selection criteria or therapeutic indications for pump therapy, apart from those for intensive therapy[1]. The pump offers greater flexibility but also poses a greater risk of complications (hypoglycemia, ketoacidosis, infections). The pump's efficacy is equivalent to that of multiple injections, but it is more expensive. Its cost-effectiveness ratio is thus twice that of multiple injections.
	[NICE, 2003]	
Recommendations	Insulin pump therapy is recommended as an option for people with type 1 diabetes provided that: • multiple daily injection (MDI) therapy (including, where appropriate, the use of insulin glargine) has failed (see Table C-1 for detailed criteria); and • those receiving the treatment have the commitment and competence to use the therapy effectively. Therapy should be initiated only by a trained specialist team, and the patient be provided with specific training in its use. The same recommendations apply to adults, children, adolescents and pregnant women. **Reimbursement policy** NICE recommends that the pump and supplies be covered under the conditions listed above.	Review the issue from a societal perspective: • Broaden access to adequate intensive therapy for all type 1 diabetics and reserve the insulin pump for a selected clientele. • Promote research to determine, among other things, the effectiveness of intensive therapy by multiple injections and of pump therapy. • Draft pump therapy protocols: period of intensive self-monitoring prior to pump use, treatment with multiple injections prior to pump use, trial period with the pump with equipment rental, etc. • Promote a funding and coverage policy aimed at achieving better metabolic control in order to reduce the incidence and prevalence of complications. **Reimbursement policy** Management of the program by accredited hospitals, with centralization of purchasing. Partial or total coverage of the pump and supplies.

1. The indications for pump therapy have changed since the AATRM report was published (personal communication from the author, August 2004).

TABLE A-2

Randomized, controlled adult trials

AUTHORS, YEAR, TYPE OF STUDY	STUDY POPULATION, DURATION, TYPE OF INSULIN	RESULTS	CONCLUSION
Pump versus multiple injections with NPH			
DeVries et al., 2002 Randomized, parallel-group trial	N = 79 patients with poor glycemic control ($HbA_{1c} \geq$ 8.5%) Duration: 16 weeks Pump: Aspart Multiple injections: NPH and aspart	**HbA_{1c} level** (observed change): Pump: - 0.91 ± 1.28% Multiple injections: - 0.07 ± 0.70% Difference of 0.84% (-1.31 to - 0.36); $p = 0.002$ **Mean blood glucose level:** Blood glucose profiles: NS **Severe hypoglycemic episodes:** NS Pump: 3 Multiple injections: 6 **Ketoacidosis:** 1 episode in each group **Quality of life (SF-36):** pump vs. multiple injections General health: + 5.9 vs. - 1.2 ($p = 0.048$) Mental health: + 5.2 vs. - 0.6 ($p = 0.05$)	In patients with a history of poor glycemic control, the pump improves the HbA_{1c} and certain aspects of quality of life. The pump should be offered to such patients when there is readiness to change.
Pump versus multiple injections with glargine (abstracts)			
Bode et al., 2003 Randomized, crossover trial	N = 100 pump-treated patients Duration: 5 weeks Pump: Aspart Multiple injections: Glargine and aspart	**HbA_{1c}** level not measured **Mean blood glucose level** (AUC $\geq$ 80 mg/dL) measured by 48-hour continuous monitoring: Pump: 2,059 ± 1,310 mg/dL/hr Multiple injections: 2,687 ± 1,734 mg/dL/hr ($p < 0.01$) **Severe hypoglycemic episodes (during the study):** Pump: 2 Multiple injections: 3	Pump therapy reduces the blood glucose level more than multiple injections with glargine without increasing the risk of hypoglycemic episodes.
Bolli et al., 2004 Randomized, parallel-group trial	N = 57 Duration: 6 months Pump: Lispro Multiple injections: Glargine and lispro	**HbA_{1c} level** (at the start and end of treatment): Pump: From 7.7 ± 0.7 to 7.0 ± 0.8% Multiple injections: From 7.8 ± 0.6 to 7.2 ± 0.7% Difference of - 0.1% (95% CI : - 0.5 to 0.3): NS **Mean blood glucose level:** Pump: From 164 ± 41 to 146 ± 32 mg/dL Multiple injections: From 160 ± 30 to 144 ± 20 mg/dL Difference of 1 (-14, 15) mg/dL: NS **Severe hypoglycemic episodes:** Too infrequent (2 episodes)	Pump therapy and multiple injection therapy with glargine lead to a similar improvement in glycemic control. Multiple injection therapy with glargine is less expensive and is therefore more cost-effective in a unselected population of type 1 diabetics.

NS: Difference not significant

TABLE A-3

Nonrandomized adult studies

AUTHORS, YEAR, TYPE OF STUDY	STUDY POPULATION, DURATION, TYPE OF INSULIN	RESULTS	CONCLUSION
Pump versus multiple injections with NPH (cohort studies)			
Hissa et al., 2002 Prospective cohort study	N = 29 Duration: 18 months Pump: Lispro Multiple injections: NPH and lispro	**HbA_{1c} level** (at baseline and at 18 months): Pump: From 8.3 ± 1.1 to 6.5 ± 0.5% ($p < 0.001$) Multiple injections: From 7.6 ± 0.8 to 7.5 ± 0.5% (NS) Difference between the groups: $p < 0.001$ **Severe hypoglycemic episodes:** None **Ketoacidotic episodes**: None	Insulin lispro permits better glycemic control with the pump than with multiple injections.
Abstract			
Cersosimo et al., 2002 Cohort study	N = 85 Duration: 24 months Type of insulin: NA	**HbA_{1c} level** (at baseline and at 24 months): Pump: From 8.0 ± 1.2 to 7.1 ± 1.1% Multiple injections: From 8.6 ± 1.6 to 8.1 ± 1.0% ($p < 0.05$) **Severe hypoglycemia** (number of episodes per patient per year): Pump: 0.30 Multiple injections: 0.46 ($p < 0.05$) **Ketoacidotic episodes**: NS	Pump therapy substantially improves clinical outcomes.

TABLE A-3.

Nonrandomized adult studies (Cont'd)

AUTHORS, YEAR, TYPE OF STUDY	STUDY POPULATION, DURATION, TYPE OF INSULIN	RESULTS	CONCLUSION
Pump versus multiple injections with glargine (cohort studies)			
Garg et al., 2004 Retrospective cohort study	N = 515 Mean duration of follow-up: 11.6 months with the pump, 13.1 months with multiple injections with glargine Pump: Lispro or aspart Multiple injections: Glargine and lispro or aspart	**HbA_{1c} level** (at baseline and after): Pump: From 7.7 ± 0.1 to 7.5 ± 0.1% ($p < 0.001$) Multiple injections: From 8.0 ± 0.1 to 7.7 ± 0.1% ($p < 0.001$) Difference between the groups: NS **Severe hypoglycemia** (number of episodes per patient per year): Pump: 0.4 ± 0.1 Multiple injections: 0.6 ± 0.1 Difference between the groups: NS **Ketoacidotic episodes:** 12 with the pump, none with multiple injections ($p < 0.01$)	Multiple injections with glargine lead to equally good glycemic control as the pump without increasing the frequency of severe hypoglycemic episodes. Based on cost estimates and the increase in ketoacidotic episodes with pump therapy, the authors recommend that therapy by multiple injections with glargine be administered systematically before consideration is given to pump therapy.
Lepore et al., 2004 Prospective cohort study	N = 48 patients with an HbA_{1c} level ≥ 8.0% and inadequate glycemic control Duration: 12 months Pump: Lispro Multiple injections: Glargine and lispro Compared the results obtained during one year of treatment by multiple injections with NPH and those obtained during one year of treatment by pump or multiple injections with glargine.	**HbA_{1c} level** (mean and standard deviation for four measurements during one year of treatment): Multiple injections with NPH: 9.0 ± 1.3% vs. pump: 8.0 ± 1.0% ($p < 0.001$) Multiple injections with NPH: 8.6 ± 1.1% vs. multiple injections with glargine: 7.9 ± 1.2% ($p < 0.001$) Improvement achieved with the pump vs. multiple injections with glargine: NS Pump: - 1.0 ± 0.8% Multiple injections with glargine: - 0.7 ± 0.6% **Mean blood glucose level** Blood glucose profiles: NS **Severe hypoglycemia** (number of episodes per patient per year): Multiple injections with NPH: 0.42 vs. pump: 0.17 ($p < 0.05$) Multiple injections with NPH: 0.46 vs. multiple injections with glargine: 0.21 ($p < 0.05$) Improvement achieved with the pump vs. multiple injections with glargine: NS Pump: - 0.25 ± 0.52 Multiple injections with glargine: - 0.25 ± 0.59	The pump and multiple injections with glargine improve glycemic control and reduce hypoglycemic episodes in diabetic patients who are unable to achieve satisfactory glycemic control with multiple injections with NPH. The results indicate that insulin glargine could be used by all diabetics with an HbA_{1c} level > 7%.

Nonrandomized adult studies (Cont'd)

Case series pre- and post-pump			
Bruttomesso et al., 2002 Retrospective case series	N = 138 patients with poor glycemic control Mean duration of pump therapy: 7.4 ± 0.4 years Type of insulin: NA	**HbA_{1c} level** (at baseline and at 12 months): From 9.3 ± 0.2 to 7.9 ± 0.1% ($p < 0.0001$) **Severe hypoglycemic episodes:** From 0.31 ± 0.07/year to 0.09 ± 0.02/year ($p < 0.003$) **Ketoacidotic episodes:** From 0.41 ± 0.12/year to 0.11 ± 0.03/year ($p < 0.013$) **Infections:** 0.2 ± 0.04/patient/year **Quality of life** (DQOL score on a 100-point scale): 73 ± 1.8 after 7 years of pump use	The pump improves the HbA_{1c} level, decreases ketoacidotic events and severe hypoglycemic episodes, and permits good quality of life.
de Borst and Berghout, 2003 Retrospective case series	N = 36 patients (type 1 diabetes) with poor glycemic control Duration: 3 months Type of insulin: NA	**HbA_{1c} level** (at baseline and at 3 months): From 8.2 ± 1.2 to 7.3 ± 1.0% ($p = 0.0005$)	Three months after the switch to pump therapy, the HbA_{1c} level was lower than during the previous treatment with multiple injections. The decrease was significant.
Garmo et al., 2004 Case series	N = 23 Duration: 6 months Type of insulin: Lispro	**HbA_{1c} level** (at baseline and at 6 months): From 6.9 to 5.9% ($p < 0.0001$)	Glycemic control, as measured by the HbA_{1c} level, improved significantly during the first 6 months of pump therapy.
Hunger-Dathe et al., 2003 Case series	N = 165 patients who were starting pump therapy Duration: 1.03 ± 0.27 years Type of insulin: NA	**HbA_{1c} level** (at baseline and at 12 months): From 7.9 to 7.35% ($p < 0.0001$) **Severe hypoglycemia** (number of episodes per patient per year): From 0.47 to 0.13 ($p = 0.007$) **Ketoacidosis** (number of episodes per patient per year): From 0.067 to 0.012 ($p = 0.06$)	The pump provides benefits to motivated patients, and therapy can be initiated at smaller centres, where the number of diabetics warrants group education.
Linkeschova et al., 2002 Case series involving different indications: need for flexibility (NF) and recurrent hypoglycemia (RH)	N = 58 (NF) N = 42 (RH) Duration: 1.8 ± 1.2 years Type of insulin: Regular	**HbA_{1c} level** (at baseline and at 12 months): NF: From 7.8 ± 1.2 to 7.2 ± 0.8% ($p < 0.05$) RH: From 7.6 ± 1.1 to 7.2 ± 1.2% ($p < 0.05$) **Severe hypoglycemia** (number of episodes per patient per year) : NF: From 0.00 to 0.02 (NS) RH: From 1.67 to 0.12 ($p < 0.05$) **Ketoacidosis**: NS **Quality of life** (DSQOLS) (pre- and post-pump): Significant improvement	The pump decreased the incidence of severe hypoglycemia in the group for which the indication was recurrent hypoglycemic episodes and resulted in better glycemic control. It also seems to have improved the quality of life.
Rudolph and Hirsch, 2002 Retrospective case series	N = 107 Duration: 36 ± 25 months Type of insulin: Lispro in 90% of the cases	**HbA_{1c} level** (pre- and post-pump): From 7.6 ± 1.5 to 7.1 ± 1.1% ($p < 0.0001$) **Severe hypoglycemic episodes:** 73% decrease ($p = 0.0003$)	The pump improved glycemic control and reduced the frequency of severe hypoglycemic episodes. This option should be offered to selected patients.

NA: Data not available; NS: Difference not significant.

TABLE A–4

Excluded publications (adults)

Armstrong and King, 2002: Abstract of a study of glycemic fluctuations between multiple injections with glargine and the pump.

Bode et al., 2002b: Comparison of insulin aspart and insulin lispro.

Catargi et al., 2001: Comparison of nonprogrammable and programmable pumps.

Harmel and Mathur, 2004: Abstract of a retrospective case series. The pre-pump therapy blood glucose values are not given.

Hayes et *al*., 2003: Abstract of a 25-patient cohort study. The duration of follow-up is not indicated.

Kamoi et al., 2004: Study of the effect of insulin lispro versus regular insulin on quality of life.

King and Armstrong, 2003: Letter to the editor concerning a study involving a series of 19 cases where the indicator mentioned is glycemic fluctuations during monitoring.

Lenhard and Maser, 2003: Abstract of the results of a trial of the pump involving 13 patients with multiple problems.

Mathur et al., 2002: Retrospective review of randomly selected charts with insufficient data.

Mathur and Harmel, 2003: Abstract of a cohort study of insulin glargine. Lack of pretreatment data.

Meyer et al., 2002: Abstract of a study of continuous blood glucose monitoring with an external pump, a peritoneal pump and multiple injections.

Pozzilli et al., 2003: Randomized study involving 19 newly diagnosed patients (same study as the abstract published by Manfrini in 2002).

TABLE A-5

Randomized pediatric trials

AUTHORS, YEAR, TYPE OF STUDY	STUDY POPULATION, DURATION, TYPE OF INSULIN	RESULTS	CONCLUSION
		Pump versus multiple injections with NPH	
Cohen et al., 2003a Randomized crossover trial	N = 16 adolescents aged 14 to 18 years (only 12 patients completed the study) Duration: 1 year Dropout rate during the study: 25% Pump: Lispro Multiple injections: NPH and regular insulin	**HbA_{1c} level** (at baseline and at the end of treatment): NS Pump: From 8.58 ± 0.82 to 8.15 ± 1.3% Multiple injections: From 8.48 ± 1.4 to 8.57 ± 0.44% **Mean blood glucose level:** NA **Severe hypoglycemia** (number of episodes per group): Pump: 1 Multiple injections: 4 **Ketoacidosis:** 1 episode with the pump **Quality of life:** The DQOLY score (satisfaction subscale) indicated a significant improvement in the pump-treated patients ($p < 0.05$); the other two subscales (worry and impact) showed similar results.	The pump is an appropriate and safe treatment and is as effective as multiple injections in adolescents. In addition, it improves certain aspects of quality of life.
Weintrob et al., 2003 and 2004a Randomized crossover trial	N = 23 patients aged 8 to 14 years Duration: 3.5 months for each treatment: 1) Glycemic control [2003] 2) Continuous blood glucose monitoring (glycemic patterns) [2004a] Pump: Lispro Multiple injections: NPH and regular insulin	**HbA_{1c} level** (at baseline and at the end of treatment): NS Pump: From 8.0 ± 1.1 to 8.0 ± 0.7% Multiple injections: From 8.3 ± 0.7 to 8.1 ± 0.8% **Mean blood glucose level:** NS Pump: 187 (36) mg/dL Multiple injections: 191 (45) mg/dL **Severe hypoglycemia** (number of episodes per patient per year) : NS Pump: 0.13 (0.0 - 0.4) Multiple injections: 0.39 (0.0 - 0.84) **Ketoacidotic episodes:** 0 **Quality of life:** DQOLY scores not significant	Intensive treatment with insulin therapy, whether by pump or multiple injections, is equally effective in providing good glycemic control in children aged 8 to 14 years.

TABLE A-5

Randomized pediatric trials (Cont'd)

AUTHORS, YEAR, TYPE OF STUDY	STUDY POPULATION, DURATION, TYPE OF INSULIN	RESULTS	CONCLUSION
Pump versus multiple injections with NPH (abstracts)			
Fox et al., 2002 Randomized, controlled, parallel-group trial Preliminary results	N = 10 patients under the age of 6 years Duration: 6 months Pump compared with current insulin injection therapy Type of insulin: NA	**HbA_{1c} level** (at baseline and at 3 months): NS Pump: From 8.0 ± 0.4 to 7.57 ± 0.19% Multiple injections: From 7.9 ± 0.6 to 7.17 ± 0.33% **Mean blood glucose level:** NS **Severe hypoglycemia:** Pump: 1 episode **Mean blood glucose level:** NS **Ketoacidosis:** Pump: 1 episode	The pump seems as practical and effective as multiple injections in young children.
Wilson et al., 2003 Randomized, controlled, parallel-group trial Preliminary results	N = 16 patients under the age of 6 years Duration: 28 weeks (planned length of one year) Type of insulin: NA	**HbA_{1c} level** (at baseline and at the end of treatment): NS Pump: From 8.0 ± 1.1 to 7.6 ± 0.8% Multiple injections: From 7.8 ± 1.0 to 7.6 ± 0.7% **Mean blood glucose level:** NS **Severe hypoglycemia:** 1 episode with the pump **Ketoacidotic episodes:** None **Quality of life:** DQOL scores not significant	The pump does not seem to be more beneficial than multiple injections in terms of glycemic control or the incidence of hypoglycemic episodes.
Pump versus multiple injections with glargine			
Doyle et al., 2004 Randomized, controlled, parallel-group trial	N = 32 patients aged 8 to 21 years Duration: 4 months Pump: Aspart Multiple injections: Glargine and aspart	**HbA_{1c} level** (at baseline and at the end of treatment): Pump: From 8.1 ± 1.2 to 7.2 ± 1.0% ($p < 0.02$) Multiple injections: From 8.2 ± 1.1 to 8.1 ± 1.2% (NS) Difference between the groups significant: $p < 0.05$ **Mean blood glucose level:** Before breakfast: difference between the two groups not significant All other measures: lower in the pump-treated group ($p < 0.01$) **Severe hypoglycemia** (number of episodes per group): Pump: 2 Multiple injections: 5 **Ketoacidosis** (number of episodes per group): Pump: 1 Multiple injections: 2 **Quality of life:** DQOLY scores (n = 16; 8 patients in each group) not significant at baseline or at 16 weeks	The pump-treated patients showed a significant improvement in glycemic control compared to those treated by multiple injections with glargine. The authors do, however, point out that a small number of children were followed for a short period of time.

NA: Data not available; NS: Difference not significant.

TABLE A-6

Nonrandomized pediatric studies

AUTHORS, YEAR, TYPE OF STUDY	STUDY POPULATION, DURATION, TYPE OF INSULIN	RESULTS	CONCLUSION
Pump versus multiple injections with NPH (cohort studies)			
Rami et al., 2003 Retrospective cohort study	N = 12 patients under the age of 3 years Duration: 24 months Pump-treated subjects compared with the cohort of controls who had received conventional treatment the previous year Pump: Lispro Multiple injections: NPH and regular insulin	**HbA_{1c} level** (at baseline and at the end of the study): NS Pump: From 8.5 (6.8-11.3%) to 7.3% (6.4-8.7%) Multiple injections: From 8.3 (8.0-10.1) to 7.0% (5.1-10.1%) **Mean blood glucose level:** NA **Severe hypoglycemia** (number of episodes during the study): NS Pump: 0 Injections: 3 **Ketoacidotic episodes:** 0 **Infections at the canula insertion site:** 0	The pump is safe and effective, even in very young children.
Pump versus multiple injections with glargine (cohort studies)			
Alemzadeh et al., 2004 Cohort study	N = 80 patients aged 10.1 to 17.8 years (pump offered to a highly motivated group) Duration: 12 months Pump: Lispro Multiple injections: Glargine and lispro	**HbA_{1c} level** (at baseline and at the end of treatment): Pump: From 8.4 ± 1.0 to 7.8 ± 0.8 % ($p < 0.002$) Multiple injections: From 8.5 ± 1.1 to 8.2 ± 0.9% (NS) **Mean blood glucose level:** NA **Severe hypoglycemic episodes:** Pump: From 20.6 to 8.2 /100 patients/years ($p < 0.05$) Multiple injections: From 18.8 to 7.5/100 patients/year ($p < 0.05$) **Ketoacidotic episodes:** Pump: 2 (cannula blockage) **Infections:** Pump: 3 at the cannula insertion site	Pump therapy resulted in a significant improvement in the HbA_{1c} level in all the patients. The percentage of patients who achieved their glycemic targets (HbA_{1c} level < 8.0%) was 52.5% with the pump and 47.5% with multiple injections with glargine. Both treatment modalities are superior to multiple injections with NPH or lispro.

TABLE A-6

Nonrandomized pediatric studies (Cont'd)

AUTHORS, YEAR, TYPE OF STUDY	STUDY POPULATION, DURATION, TYPE OF INSULIN	RESULTS	CONCLUSION
Pump versus multiple injections with NPH (case series)			
Hathout et al., 2003 Retrospective case series	N = 39 patients aged 10 to 20 years Duration: 12 months Pump: Lispro Multiple injections before the pump: NPH and lispro	**HbA_{1c} level** (pre- and post-pump) (mean value and confidence interval): 3 months before the pump: 8.38% (7.94-8.81) 3 months after the pump: 7.55% (7.25-7.86) Difference between the groups: $p < 0.0001$ At 9 and 12 months, the pre- and post-pump difference was not significant. **Mean blood glucose level** (mean value and confidence interval) in mg/dL: NS 12 months before pump: 184.4 (159.03-209.77) 12 months after pump: 193.40 (178.40-208.40) **Severe hypoglycemic episodes:** NA **Ketoacidotic episodes:** Frequency decreased in two patients after pump use	The initial beneficial effect of the pump on the HbA_{1c} level does not persist over time.
Liberatore et al., 2004 Retrospective case series	N = 73 patients aged 2 to 17 years (youths motivated to try the pump) Duration: 6 to 30 months Pump: Lispro	**HbA_{1c} level** (pre- and post-pump at 12 months): 8.3 ± 1.0 vs. 7.5 ± 1.1% ($p < 0.00001$) **Mean blood glucose level:** NA **Severe hypoglycemia:** 20 episodes/100 patients/year **Ketoacidosis:** 4.3 episodes/100 patients/year 23% of the children experienced a technical problem with the pump, due to which the pump had to be returned to the manufacturer.	The pump improved the HbA_{1c} level without increasing the number of hypoglycemic or ketoacidotic episodes.
Litton et al., 2002 Case series	N = 9 patients under the age of 4 years with inadequate glycemic control Duration: 12.7 months (7 to 19 months) Pump: NA Multiple injections before the pump: NPH and regular insulin or lispro	**HbA_{1c} level** (pre- and post-pump): 9.5 ± 0.4 vs. 7.9 ± 0.3% ($p < 0.001$) **Mean blood glucose level:** NA **Severe hypoglycemia:** 0.52 ± 0.1 vs. 0.09 ± 0.02 episodes/month ($p < 0.05$) **Ketoacidosis:** NS 0.06 ± 0.03 emergency room visits per month both pre- and post-pump	Pump therapy can reduce the HbA_{1c} level and the frequency of hypoglycemic episodes in preschoolers with inadequate glycemic control. Highly motivated and supervised families can administer effective and safe treatment to selected children.

Nonrandomized pediatric studies (Cont'd)

AUTHORS, YEAR, TYPE OF STUDY	STUDY POPULATION, DURATION, TYPE OF INSULIN	RESULTS	CONCLUSION
Pump versus multiple injections with NPH (case series) (Cont'd)			
Pankowska et al., 2003 Case series	N = 40 patients under the age of 10 years Duration: 24 months Type of insulin: NA	**HbA_{1c} level** (pre- and post-pump at 12 months): From 8.27 ± 1.4 to 7.37 ± 0.86% ($p < 0.05$) **Mean blood glucose level:** NA **Severe hypoglycemia:** 3 episodes **Ketoacidosis:** 2 episodes **Infections at the cannula insertion site:** 2	The insulin pump provides good and sustained glycemic control in young children.
Plotnick et al., 2003 Case series	N = 95 patients aged 4 to 18 years Duration: 6 to 12 months before the start of pump therapy and up to 48 months after (median: 28 months) Pump: Regular or lispro	**HbA_{1c} level** (pre- and post-pump at 12 months): 8.1 vs. 7.7% ($p < 0.001$) (level adjusted for age and duration of disease) The HbA_{1c} level decreased significantly between 3 and 6 months of follow-up (7.7 vs. 8.2%, $p < 0.03$), then gradually increased and remained elevated after one year. **Mean blood glucose level:** NA **Hypoglycemic episodes** (rate per 1,000 patients/month, pre- and post-pump): 14.3 vs. 6.6 (RR: 0.46; 95% CI: 0.21 to 1.01) **Ketoacidotic episodes:** NS **Infections at the cannula insertion site:** 8	The insulin pump is safe and effective in children and adolescents.
Saha et al., 2002 Case series	N = 16 patients aged 1 to 16 years selected because of hypoglycemic episodes and inadequate glycemic control Duration: 2.1 (0.4 to 4.2) years Pump: Regular insulin	**HbA_{1c} level** (pre- and post-pump): NS From 9.1 ± 2.4 to 8.7 ± 1.6% **Mean blood glucose level:** NA **Severe hypoglycemic episodes:** Decreased after pump use (8 vs. 2) **Ketoacidosis**: 1 episode before pump and 9 after	The pump resulted in better glycemic control than conventional treatment, especially in the adolescents with inadequate glycemic control ($HbA_{1c} > 10\%$) and reduced the occurrence of nocturnal hypoglycemia.
Sulli and Shashaj, 2003 Case series	N = 40 patients aged 4 to 25 years selected according to certain criteria Duration: 6 months Pump: Lispro	**HbA_{1c} level** (at baseline and at 6 months): From 9.5 ± 1.7 to 8.8 ± 1.5% ($p < 0.05$) **Mean blood glucose level** (1 month before pump and 6 months after): From 11.4 ± 2.1 to 9.0 ± 1.9 mmol/L ($p = 0.01$) **Hypoglycemia** (at baseline and at 6 months): From 6.5 ± 5.5 to 3.5 ± 3.0 episodes/patient/month ($p = 0.04$) **Ketoacidosis:** 2 episodes (0.1 episode/patient/year) **Other:** Injection site lipohypertrophy: 25% of the cases	The pump is safe and effective in children and adolescents and can improve glycemic control and reduce the risk of hypoglycemic episodes in a selected group.

TABLE A-6

Nonrandomized pediatric studies (Cont'd)

AUTHORS, YEAR, TYPE OF STUDY	STUDY POPULATION, DURATION, TYPE OF INSULIN	RESULTS	CONCLUSION
Pump versus multiple injections with NPH (case series) (Cont'd)			
Shehadeh et al., 2004 Case series	N = 15 patients aged 1 to 6 years Duration: 12 months Pump: Aspart	**HbA_{1c} level** (at baseline and at 12 months): From 8.82 ± 0.98 to 8.18 ± 0.90% ($p < 0.05$) **Mean blood glucose level:** NA **Severe hypoglycemic episodes:** NS 0.36 episodes/patient/year before the start of pump therapy and 0.29 episodes/patient/year during pump therapy **Ketoacidotic episodes:** 0 **Quality of life** (modified DQOL) (at baseline and at 4 months): 43.7 ± 8.0 vs. 33.7 ± 7.9 ($p < 0.001$)	The pump is a safe option for very young children and can improve the quality of life.
Tumini et al., 2002 Case series	N = 10 patients aged 14 to 21 years Duration: 6 months Type of insulin: NA	**HbA_{1c} level:** NS Decrease of 0.2 to 0.4% **Mean blood glucose level:** NA **Severe hypoglycemic episodes:** 75% decrease ($p < 0.01$) **Ketoacidotic episodes:** NA	The pump improved glycemic control in selected, motivated patients.
Willi et al., 2003 Case series	N = 51 patients aged 10.7 ± 3.1 years Duration: 12 months Pump: Short-acting insulin analogue	**HbA_{1c} level:** From 8.4 ± 0.2 to 7.9 ± 0.1% ($p < 0.01$) **Mean blood glucose level:** NA **Severe hypoglycemic episodes:** NA **Ketoacidotic episodes:** NA	The pump can improve glycemic control in children and reduce the occurrence of nocturnal hypoglycemia. The benefits are not as great in preadolescents.

Nonrandomized pediatric studies (Cont'd)

AUTHORS, YEAR, TYPE OF STUDY	STUDY POPULATION, DURATION, TYPE OF INSULIN	RESULTS	CONCLUSION
		Abstracts	
Buckloh et al., 2002 Case series	N = 18 patients aged 7 to 15 years Duration: 18 months Type of insulin: NA	**HbA_{1c} level** (pre- and post-pump at 18 months): From 8.0 to 7.54% ($p < 0.01$) **Mean blood glucose level:** NA **Severe hypoglycemic episodes:** NS Pump: 28.91 episodes/100 patients/year Multiple injections: 28.29 episodes/100 patients/year **Ketoacidotic episodes:** NA **Quality of life:** NS	The pump can improve glycemic control without increasing the risk of hypoglycemic episodes or affecting the quality of life.
Schiaffini, 2003 Case series	N = 15 patients aged 12.7 ± 1.8 years Duration: 12 months Type of insulin: Lispro or aspart	**HbA_{1c} level:** 9.2 ± 2.2 vs. 7.9 ± 1% ($p < 0.05$) **Mean blood glucose level:** NA **Severe hypoglycemic episodes:** NS **Ketoacidotic episodes:** NA	The pump is a safe and effective alternative for certain children.
Steijlen et al., 2004 Retrospective case series	N = 123 children and adolescents Duration: 6 months Type of insulin: NA	**HbA_{1c} level** (pre- and post-pump) From 8.3 to 7.9% (no p value) **Mean blood glucose level:** NA **Severe hypoglycemic episodes:** Decrease in 73% of the patients **Ketoacidosis:** From 6.92 to 2.27 episodes/year	The pump can improve glycemic control in children treated in private practice with no additional risk of hypoglycemia or ketoacidosis.
Weinzimer et al., 2003 Retrospective case series	N = 65 patients aged 1.4 to 6.9 years Duration: 2.5 years Type of insulin: NA	**HbA_{1c} level** (pre- and post-pump at 12 months and up to 30 months of follow-up): From 7.4 ± 1.0 to 6.9 ± 1.0% ($p < 0.001$) **Mean blood glucose level:** NA **Severe hypoglycemia:** From 78 to 37 episodes/100 patients/year ($p < 0.001$) **Ketoacidosis:** 4 episodes/100 patients/year with the pump during the 2.5 years of follow-up	The pump is an effective tool whose effect on glycemic control persists for up to one year. The pump might be superior to multiple injections in reducing the risk of severe hypoglycemic episodes in this age group.

NA: Data not available, NS: Difference not significant, RR: Relative risk

TABLE A-7

Excluded publications (children)

Burdick et al., 2004: Impact of missed mealtime boluses on the HbA_{1c} level in pump users.

Heptulla et al., 2004: Continuous blood glucose monitoring in pump users.

Hofer and Steichen, 2003: Case series (7 adolescents). No data on the mean HbA_{1c} level.

Humphrey et al., 2004: Abstract of a study of the benefit of a 6-month transition period with multiple injection therapy prior to pump therapy in children on conventional therapy.

Pinsker et al., 2003 (abstract): HbA_{1c} results are provided only as differences between the two groups. The absolute HbA_{1c} levels are not given.

Pozzilli et al., 2003: Randomized study of 19 newly diagnosed patients (same study as the abstract published by Manfrini in 2002).

Quinn et al., 2003 (abstract): Mainly newly diagnosed cases, plus a small subgroup of patients moving from multiple injections to the pump.

Ramchandani, 2003: Abstract concerning newly diagnosed cases.

Razeghi et al., 2002: Fewer than five patients.

Schiaffini et al., 2002: Abstract of a study comparing insulin lispro and insulin aspart.

TABLE A-8

Meta-analyses and assessment reports on the efficacy of the pump compared to that of multiple injection therapy

	METHOD	RESULTS	CONCLUSIONS
Colquitt et al., 2002	**Literature search**: See Appendix B. **Inclusion criteria**: RCTs comparing the pump and multiple injections **Exclusion criteria**: Comparison with conventional therapy, newly diagnosed patients, implantable pumps, very short follow-up, and hospitalized patients **Outcome measures**: HbA_{1c} level Total insulin dose Severe hypoglycemic episodes Patient preferences Costs	20 studies No RCTs with children N = 259 (adults) **Decrease in the HbA_{1c} level**: NS Short-term studies: - 0.64 (95% CI: - 1.28 to 0.01) Longer-term studies: - 0.61 (95% CI: - 1.29 to 0.07) **Total insulin dose**: - 11.9 insulin units (95% CI: - 18.16 to - 5.63)	Insulin pump technology has improved considerably since the early studies, and pumps are smaller and more reliable. RCTs show that the pump confers modest benefits. Observational studies report greater benefits, probably because the patients are selected on the basis of particular problems, with the result that their condition is more likely to improve. It is unlikely that the pump would be used by more than a small percentage of type 1 diabetics, but the exact proportion is uncertain.
Pickup et al., 2002	**Literature search**: MEDLINE (1975-2000), Embase (1980-2000), Cochrane database of RCTs, company literature, and the Internet. **Inclusion criteria**: Follow-up > 2 wks (2.5 to 24 months) **Exclusion criteria**: Studies of insulin pen infusers, newly diagnosed patients, and pregnant women. **Outcome measures**: Mean blood glucose level HbA_{1c} level Total insulin dose **Bias control**: Publication bias assessed	12 RCTs, including 11 with a crossover design N = 600 (301 treated by pump and 299 treated by multiple injections) The trials that provide HbA_{1c} and total insulin dose data and which were combined by meta-analysis are heterogenous. The trials examining blood glucose levels are homogenous. The longer-term trials tend to show a greater difference in glycemic control. **Standardized mean difference in the blood glucose level**: 0.56 (95% CI: 0.35 to 0.77), equivalent to 1.06 mmol/L in absolute units **Decrease in the HbA_{1c} level:** 0.44 (95% CI: 0.20 to 0.69), equivalent to a difference of 0.51% in absolute units **Variability in the blood glucose level:** Significantly higher in the group treated by multiple injections **Total insulin dose:** Mean reduction of 14% with the pump (difference in the total insulin dose of 0.58 (95% CI: 0.34 to 0.83), equivalent to 7.8 insulin units per day	The pump is an effective form of intensive therapy. Glycemic control is slightly but significantly better. The pump should be reserved for patients with special problems, such as unpredictable hypoglycemia or pronounced morning hyperglycemia, despite attempts to improve control with intensive therapy by multiple injections.

RCTs: Randomized controlled trials, CI: confidence interval; NS: Difference not significant

APPENDIX B: SEARCH STRATEGY

INFORMATION SOURCES AND DATABASES QUERIED ON INSULIN PUMPS

The searches were executed in September 2003 and updated in June 2004 and covered, for the most part, the period from 2001 to 2004.

INFORMATION SOURCE OR DATABASE QUERIED	TERMS USED
NLM Gateway, including **NLM Locator plus, PubMed, Meetings Abstracts, Clinical Trials**	Insulin pump* OR csii OR insulin infusion
CINAHL	(Insulin NEAR pump*) OR csii OR (insulin NEAR infusion)
COCHRANE Library, including **DARE, HTA, NHS EED**	(Insulin NEAR pump*) OR csii OR (insulin NEAR infusion)
Dissertation Abstract, EconoLit, Science Citation Index, Current Contents (Clinical Medicine)	insulin(w)pump* OR csii OR insulin(w)infusion
Web of science & Biosis	(Insulin pump* OR csii OR insulin infusion) AND random*
MEDLINE, Embase and **Pascal**	insulin(3n)pump? OR (pump?(w)therapy and diabet?) OR csii OR ((subcutaneous OR continuous)(w)insulin(w)infusion) OR (external(w)pump(2n) (diabet? OR insulin))
Catalogues of various **libraries** in Australia, Canada, the United States and Europe	
Internet searches using several different search engines: Google, AltaVista, Fast, HotBot, Teoma, Francité, Nomade, Voilà, etc.	Insulin pump, insulin pumps, csii, insulin infusion, pompe insuline, insuline infusion, infusion diabetes, infusion diabete
Canadian (**Health Canada**) and American (**FDA**) medical device approval databases or incident reports concerning the use of these devices	

APPENDIX C: EXAMPLES OF PUMP COVERAGE AND PATIENT SELECTION CRITERIA

TABLE C-1

Examples of indications and coverage criteria

NICE, 2003

People with type 1 diabetes for whom multiple daily injection (MDI) therapy (including, where appropriate, the use of insulin glargine,) has failed.

People for whom MDI therapy has failed are considered to be those for whom it has been impossible to maintain a haemoglobin A_{1c} level no greater than 7.5% (or 6.5% in the presence of microalbuminuria or adverse features of the metabolic syndrome) without disabling hypoglycaemia occuring, despite a high level of self care of their diabetes. 'Disabling hypoglycaemia' means the repeated and unpredictable occurrence of hypoglycaemia requiring third-party assistance that results in continuing anxiety about recurrence and is associated with significant adverse effect on quality of life.

People who have the commitment and competence to use the therapy effectively.

Centers for Medicare & Medicaid Services, 2000

For the pump to be covered (effective for services performed on or after April 1, 2000), patients must:

- have completed a comprehensive diabetes education program;
- have been self-administering multiple injections (at least three per day) for at least six months;
- have had to make frequent self-adjustments of their insulin dose for at least six months prior to initiation of pump therapy;
- have a documented frequency of glucose self-testing of an average of at least four times per day in the previous two months;
- meet one or more of the following criteria while on the multiple daily injection regimen:
  - HbA_{1c} level > 7%;
  - a history of recurring hypoglycemia;
  - wide fluctuations in the blood glucose level before mealtime;
  - dawn phenomenon, with fasting blood glucose levels frequently exceeding 200 mg/dL;
  - a history of severe glycemic excursions;

OR have been on a pump prior to enrolment in Medicare and have a documented frequency of glucose self-testing of an average of at least four times per day during the month prior to Medicare enrolment.

Note: Diabetes needs to be documented by a fasting C-peptide level $\leq$ 110% of the lower limit of normal of the laboratory's measurement method.

Office of Medicaid Management, 2001

- Inadequate glycemic control
- Frequent hypoglycemia
- Dawn or Somogyi phenomenon
- Active or athletic
- Demanding lifestyle
- Does shift work
- Is planning a pregnancy
- Complications such as gastroparesis
- Motivated to achieve better glycemic control, willing to follow through with a diabetes treatment plan (blood glucose testing four times a day) and a meal plan, and regularly attends his/her follow-up appointments

TABLE C-2

Examples of patient selection criteria

ADULTS

Bode et al., 2002a

- Inadequate glycemic control (HbA_{1c} level > 7%)
- Dawn phenomenon with blood glucose levels > 8-9 mmol/L
- Marked variability in the blood glucose level
- History of hypoglycemia unawareness or of hypoglycemic events requiring immediate assistance
- Need for flexibility in lifestyle
- Pregnancy or intention to become pregnant
- Low insulin requirements (< 20 U per day)

Pickup et al., 2002; Pickup and Keen, 2002

The pump is recommended when, despite optimal multiple injection therapy:

- glycemic control is inadequate;
- the patient experiences unpredictable hypoglycemia;
- there is a marked dawn blood glucose rise;
- the patient experiences erratic swings in the blood glucose level or has an erratic lifestyle;
- the patient is pregnant and has inadequate glycemic control.

CHILDREN

Cogen et al., 2002

- At least 10 years of age
- 3 to 6 months of three or more injections per day
- 3 to 6 months of monitoring and recording blood glucose levels at least four times per day
- Ability to self-administer abdominal injections (not afraid of needles)
- Ability to make small adjustments in treatment regimen between visits
- Evidence of diabetes team contact in emergency situations
- Adequate insurance coverage
- Psychosocial requirements:
  - Psychologist visit to assess pump readiness
  - Child/adolescent responsibility for the majority of diabetes self-care
- Dietitian visit
- 3 to 6 months of carbohydrate counting

Litton et al., 2002

Preschool children who have had diabetes for at least six months and who have one or more of the following problems while on multiple injection therapy:

- HbA_{1c} level > 9% and remaining elevated despite frequent adjustments to the insulin dose
- Frequently recurring episodes of moderate or severe hypoglycemia
- Erratic and unpredictable swings in the blood glucose level that do not resolve with adjustments to the insulin dose
- Recurrent ketoacidosis or severe hyperglycemic episodes that are not due to poor therapeutic compliance

Examples of patient selection criteria (Cont'd)

CHILDREN (Cont'd)

Sulli and Shashaj, 2003

Unstable diabetes

Elevated HbA_{1c} level

Recurring hypoglycemic episodes

Dawn phenomenon

Early microvascular complications

Difficulty coordinating injections with meals because of an irregular meal schedule

Tamborlane et al., 2003

Potential reasons for adopting pump therapy:

- Young or small child
- School-age child who wants to try the pump
- Large and unpredictable glycemic fluctuations
- Nocturnal hypoglycemia
- Need for greater flexibility for sports or because of an irregular meal schedule

Pump therapy eligibility criteria:

- Ability to perform four blood glucose measurements per day
- Motivated to undertake intensive therapy
- Family is knowledgeable about diabetes and provides support
- Regular attendance at follow-up visits
- No unrealistic expectations
- Ability to count carbohydrates
- Understanding of diabetes self-management
- Inability to achieve adequate diabetic control with multiple injections (HbA_{1c} level < 9%)

APPENDIX D: THE PATIENT PERSPECTIVE

PATIENT QUESTIONNAIRE

Montréal, le 18 décembre 2003

Madame,
Monsieur,

Je vous remercie d'avoir accepté l'invitation de l'Agence d'évaluation des technologies et modes d'intervention en santé (AETMIS) à partager votre expérience avec la pompe à insuline (pour ceux qui l'utilisent) ou votre opinion la concernant (non-utilisateurs), en répondant au questionnaire ci-joint. L'AETMIS (www.aetmis.gouv.qc.ca) est un organisme indépendant relevant du ministre de la Santé et des Services sociaux du Québec. Sa mission est de conseiller le ministre et d'appuyer, au moyen de l'évaluation, les décideurs du milieu québécois de la santé. Ses évaluations portent sur l'introduction, l'acquisition et l'utilisation de technologies de la santé, ainsi que sur les modalités de dispensation et d'organisation des services.

Le Ministère de la Santé et des Services sociaux a mandaté l'AETMIS pour préparer un rapport d'évaluation sur la pompe à insuline. Ce rapport sera disponible au printemps 2004. Les éléments d'analyse du rapport couvriront la sécurité de la pompe à insuline, son efficacité et son efficience (en comparaison avec le traitement par multi-injections d'insuline) et la perspective des patients et des professionnels.

Vos réponses au questionnaire serviront à décrire la perspective des patients québécois, pour enrichir le rapport d'évaluation sur la pompe à insuline. Pour des fins de suivi ou pour vous demander des informations supplémentaires, s'il y a lieu, votre nom serait utile, mais il n'est pas obligatoire. Dans tous les cas, le traitement des informations assurera votre anonymat.

Le questionnaire complété peut m'être retourné par courriel ou par facsimilé. Malheureusement, le questionnaire est disponible seulement en version française.

Merci de votre collaboration,

Dre Brigitte Côté
Tél :(514) 864-1037
Fax : (514) 873-1369
Courriel brigitte.cote@ aetmis.gouv.qc.ca

1) Nom du répondant (facultatif) :

2) Êtes-vous ☐ patient diabétique
☐ parent d'enfant diabétique
☐ autres* (précisez) :

3) Âge actuel (du patient diabétique) : ans Sexe
F ☐ M ☐

4) Âge au diagnostic de la maladie : ans

5) Type de traitement **actuel** :
☐ Pompe à insuline
☐ Injections d'insuline, combien par jour :
si injections, combien par jour :

6) Depuis quand êtes vous sur le traitement actuel :
☐ moins d'un an
ans

7) **Dans le mois précédent le traitement actuel**, quel traitement aviez-vous :
☐ Aucun
☐ Pompe à insuline
☐ Injections d'insuline
si injections, combien par jour :

Si vous avez actuellement une pompe à insuline, passez à la question 8)
Si vous n'utilisez pas la pompe actuellement, passez à la question 15)

8) Quelle est **la raison principale** ayant motivé votre changement à ce traitement (**pompe à insuline**) :
☐ Améliorer l'hémoglobine glyquée (taux de sucre dans le sang)
☐ Hypoglycémies sévères nécessitant le recours aux services de santé
☐ Hypoglycémies symptomatiques
☐ Hyperglycémies nécessitant le recours aux services de santé
☐ Hyperglycémies symptomatiques
☐ Hyperglycémies matinales
☐ Aspects psychologiques
☐ Désir de flexibilité des activités sportives
☐ Désir de flexibilité de la diète
☐ Désir de flexibilité des horaires
☐ Autre raison (l'inscrire SVP) :
Commentaires sur la raison principale (optionnel) :

*Le présent questionnaire ne s'adresse qu'aux patients diabétiques ou aux parents d'enfants diabétiques.

9) Quelle est **la deuxième raison principale** ayant motivé votre changement à ce traitement :

- ☐ Aucune autre raison que la raison principale
- ☐ Améliorer l'hémoglobine glyquée (taux de sucre dans le sang)
- ☐ Hypoglycémies sévères nécessitant le recours aux services de santé
- ☐ Hypoglycémies symptomatiques
- ☐ Hyperglycémies nécessitant le recours aux services de santé
- ☐ Hyperglycémies symptomatiques
- ☐ Hyperglycémies matinales
- ☐ Aspects psychologiques
- ☐ Désir de flexibilité des activités sportives
- ☐ Désir de flexibilité de la diète
- ☐ Désir de flexibilité des horaires
- ☐ Autre raison (l'inscrire SVP) :

Commentaires sur la deuxième raison principale (optionnel) :

10) Parmi les aspects suivants, lesquels selon vous ont été améliorés par l'utilisation de la pompe à insuline :

- ☐ L'hémoglobine glyquée (taux de sucre dans le sang)
- ☐ Hypoglycémies sévères nécessitant le recours aux services de santé
- ☐ Hypoglycémies symptomatiques
- ☐ Hyperglycémies nécessitant le recours aux services de santé
- ☐ Hyperglycémies symptomatiques
- ☐ Hyperglycémies matinales
- ☐ Aspects psychologiques
- ☐ Désir de flexibilité des activités sportives
- ☐ Désir de flexibilité de la diète
- ☐ Désir de flexibilité des horaires
- ☐ Autre aspect (l'inscrire SVP) :

11) Êtes vous couvert par une assurance médicale privée pour la pompe

- ☐ oui
- ☐ non

si oui :

Quel est le pourcentage de couverture ?

pour la pompe :

pour les fournitures :

Y a-t-il des limites pour les réclamations auprès de votre assureur :

- ☐ oui
- ☐ non

si oui, quelles sont-elles :

12) Quels sont les avantages selon vous du traitement par pompe :

13) Quels sont les désavantages selon vous du traitement par pompe :

14) Avez vous vécu un incident en lien avec votre pompe (technique ou autre) ?

15) Avez-vous l'intention de continuer le traitement sous pompe ?

☐ oui

☐ non si non, pourquoi?

À répondre seulement si vous ne portez pas de pompe actuellement

16) Avez-vous déjà porté une pompe ?

☐ Oui (si oui, passez à la question 18)
☐ Non (si non, passez à la question 17)

17) Désirez vous adopter le traitement par pompe?

☐ non
☐ oui

si oui, quel est le principal obstacle à l'adoption de la pompe ?

Passez à la question 21

18) Si oui, quelle est la raison principale ayant motivé à délaisser le traitement par pompe ?

19) Quels sont les avantages selon vous du traitement par pompe :

20) Quels sont les désavantages selon vous du traitement par pompe :

Pour tous les répondants :

21) À quel centre hospitalier êtes-vous suivi actuellement :

22) Quelle a été votre première source d'information sur la pompe à insuline :

☐ votre médecin de famille
☐ votre médecin endocrinologue
☐ un autre membre de l'équipe professionnelle soignante

si oui, précisez :

☐ l'internet
☐ des livres ou revues
☐ une autre personne diabétique
☐ un groupe communautaire de soutien
☐ mon entourage
☐ autre source : (l'inscrire SVP) :

23) Quelle formation à l'utilisation de la pompe vous a été offerte ?

Veuillez décrire chaque personne-ressource (médecin, infirmière, représentant, etc.) combien de temps en tout et dans quel lieu.

Par exemple :
Personne-ressource : **l'infirmière**
Nombre de sessions : **3 sessions**
Durée moyenne: **1 heure**
Lieu : **clinique externe**

☐ Je n'ai pas été formé **Passez à la question 24**
☐ Je ne suis pas utilisateur **Passez à la question 25**

Personne-ressource :
Nombre de sessions :
Durée moyenne :
Lieu :

Personne-ressource :
Nombre de sessions :
Durée moyenne :
Lieu :

Personne-ressource :
Nombre de sessions :
Durée moyenne :
Lieu :

Personne-ressource :
Nombre de sessions :
Durée moyenne :
Lieu :

24) Avez-vous accès à du soutien additionnel ?

☐ Oui si oui, ☐ famille
☐ amis
☐ groupe d'entraide
☐ autres :

☐ Non

25) Autres commentaires ou témoignages (optionnel)
(Cette section permet le recueil d'information qualitative qui n'aurait pas été capturée par les questions plus haut) :

26) Cochez l'expression qui représente le mieux votre scolarité (optionnel) :

- ☐ Primaire complété
- ☐ Secondaire complété
- ☐ Collégial complété
- ☐ Degré universitaire complété (premier cycle)
- ☐ Études universitaires de deuxième cycle complétées

27) Quel a été votre revenu annuel familial en 2002 (optionnel) :

- ☐ moins de 20 000 $
- ☐ 20 à 40 000 $
- ☐ 40 à 60 000 $
- ☐ 60 à 80 000 $
- ☐ 80 à 100 000 $
- ☐ 100 000 $ et plus

MERCI de votre participation

TABLE D-1

Sociodemographic data on the survey's respondents

SOCIODEMOGRAPHIC DATA	ADULTS	PARENTS OF DIABETIC CHILDREN
Number	23	11
Mean age of the diabetic	36 years (17-56)	7 years (4-12)
Mean duration of diabetes	20 years (1-30)	3 years (1-8)
Pump used for more than a year	60%	30%
Collegial education completed	9/21 (42.9%)	4/11 (36.4%)
University education completed	9/21 (42.9%)	7/11 (63.7%)
Average annual income	52.6% ≥ 60,000	80% ≥ 60,000
Private insurance covering pump and supplies	95%	100%

TABLE D-2

Reasons for adopting the pump and improvements noted by patients

COMMENTS	ADULTS (N = 20)		PARENTS OF DIABETIC CHILDREN (N = 10)	
	REASONS GIVEN	IMPROVEMENT NOTED	REASONS GIVEN	IMPROVEMENT NOTED
Improvement in the HbA_{1c} level	12	16	10	7
Severe hypoglycemia requiring the use of health-care services	7	7	1	3
Symptomatic hypoglycemia	5	10	4	6
Hyperglycemia requiring the use of health-care services	1	6	-	2
Symptomatic hyperglycemia	2	12	4	6
Morning hyperglycemia	7	15	1	6
Psychological reasons	4	13	4	9
Desire for flexibility with regard to sports	3	10	3	6
Desire for flexibility in diet	2	11	4	9
Desire for flexibility in schedules	6	12	3	9
Other:	8*	12†	4*	5†

* The other reasons given for adopting the pump were very frequent, asymptomatic hypoglycemic episodes, glycemic fluctuations, a high creatinine level, a research project (proposal by the endocrinologist), injection site problems, a planned pregnancy, and difficulty in adjusting the insulin dose.

† The other improvements noted were a decrease in infections, less stress in the family members, disappearance of the anxiety associated with poor diabetic control.

APPENDIX E: THE HEALTH PROFESSIONAL PERSPECTIVE

INTERVIEW GUIDE FOR HEALTH PROFESSIONALS

Bonjour, la présente rencontre a pour but de connaître votre perception sur l'usage de la pompe à insuline dans une clientèle adulte (ou pédiatrique), pour mieux comprendre le contexte québécois des soins aux diabétiques de type 1 et alimenter le rapport bref d'évaluation de l'Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS).

L'AETMIS est un organisme indépendant relevant du ministre de la Santé et des Services sociaux du Québec. Sa mission est de conseiller le ministre et d'appuyer, au moyen de l'évaluation, les décideurs du milieu québécois de la santé. Ses évaluations portent sur l'introduction, l'acquisition et l'utilisation de technologies de la santé, ainsi que sur les modalités de dispensation et d'organisation des services.

Vous avez reçu du matériel préparatoire à la rencontre, concernant certains éléments de la littérature médicale et de la perspective du patient. Ce matériel servira de point de départ à la discussion.

Les questions à l'ordre du jour sont :

1) Le traitement par pompe à insuline est-il sécuritaire, efficace, efficient en comparaison avec les multiples injections journalières, chez les adultes (ou chez les enfants) ?

2) Quels sont selon vous les avantages comparatifs ou les inconvénients pour vos patients ?

3) Quelle est votre vision de l'utilisation clinique de la pompe dans votre clientèle de patients ? Ceci comprend les critères cliniques, les impératifs de formation, les aspects administratifs et finalement les défis d'organisation des services.

4) Considérant les ressources humaines disponibles, selon vous au Québec en diabète de type 1, quelle est votre vision de la meilleure utilisation de ces ressources ?

MERCI de votre participation

DATE _____ MILIEU _____

Décrivez l'équipe qui travaille avec les diabétiques de type 1.
À combien de patients environ estimez vous votre clientèle de la clinique ? Combien avec pompe ?

Et les autre établissements impliqués au niveau de la pompe selon vous ? Y a-t-il de l'information sur des volumes de clientèle ? De nombre de patients sous pompe ?

1) Sécurité, efficacité, efficience

   - sécuritaire en comparaison avec les multiples injections journalières
   - efficace en comparaison avec les multiples injections journalières,
   - efficient en comparaison avec les multiples injections journalières

2) Avantages comparatifs ou désavantages selon vous pour les patients ?

3) Votre vision de l'utilisation clinique de la pompe dans votre clientèle de patients.
Ceci comprend les critères cliniques, les impératifs de formation, les aspects administratifs et finalement les défis d'organisation des services.
   - critères cliniques
     À qui, quels critères, processus de sélection ?
     Avez-vous des outils ?
   - ressources et formation
     Quelles ressources sont existantes ?
     Quel type de formation serait nécessaire ?
     Existe-t-il des formations reconnues ?
   - administratifs, (soutien nécessaire, ressources humaines et financières)
   - défis d'organisation des services (accès, location d'équipements, équité régionale) et les solutions selon vous ?

4) Si vous pensez aux ressources humaines disponibles selon vous au Québec en diabète de type 1, nous allons discuter de votre vision de la meilleure utilisation de ces ressources.

Quels sont les besoins prioritaires des diabétiques de type 1 selon vous ?
Comment se situe l'accès à la pompe dans l'ensemble de ces besoins ?

Si l'on pense maintenant à l'ensemble des patients souffrant de diabète de type 1 et 2, quels sont selon vous les besoins prioritaires ?
Comment se situe l'accès à la pompe dans ces besoins prioritaires ?

MERCI

TABLE 6.6

Criteria*, mentioned by the clinical care teams in Québec, for selecting patients who will benefit from the pump†

The adult care teams agree on the following criteria:

- Inadequate glycemic control (HbA_{1c} level greater than 8%), despite an attempt at intensive insulin therapy (with the patient already self-administering four to seven injections per day) and excellent basic training on intensive insulin therapy with injections
- Recurrent severe hypoglycemia (twice or more per year)
- Asymptomatic or nocturnal hypoglycemia
- Blood glucose measurement at least four times a day
- Patient motivated and serious about trying the pump
- No false hopes or illusions about the pump
- Ability to understand how to use the pump and how to adjust his/her insulin doses
- Ability to communicate with the care team and good therapeutic compliance
- Need for flexibility because of lifestyle or irregular schedule
- Ability to pay

The pediatric care teams also agree on the clinical criteria for guiding the decision to use or not use the pump:

INDICATIONS	CONTRAINDICATIONS
▪ Motivated parents and child who make the effort	▪ New patient (it takes six months to one year of injection therapy before the pump can be proposed)
▪ Parents or child who do or does at least three blood glucose measurements a day	▪ Remission phase
▪ Parent is reasonably able to make calculations	▪ Child with learning problems
▪ Dawn phenomenon	▪ Frequent diabetic ketoacidosis
▪ Nocturnal hypoglycemia	▪ Youth rebelling against his/her disease
▪ Hypoglycemic insensitivity	▪ Family or psychological problems (anorexia, bulimia)
▪ Very young children (under 18 months of age), since they require very small doses and have a special diet. Furthermore, hypoglycemia is more worrisome at this age	▪ Resistance to changing the injection site
	▪ Extreme parental fear of hypoglycemia

* The exclusion criteria are the opposite of the inclusion criteria and are therefore not repeated.
† Criteria mentioned by all the clinical care teams consulted during the interviews conducted in Québec in 2003 for the purpose of this report.

APPENDIX F: ECONOMIC STUDIES OF INSULIN PUMP THERAPY

TABLE F-1

Economic studies

AUTHORS	Scuffham and Carr, 2003	Roze et al., 2002 Abstract	Roze and Palmer, 2002 Abstract	De Sola-Morales et al., 2004 Conference paper (forthcoming AATRM publication)
TYPE OF ANALYSIS	8-year Markov model Monte Carlo simulation (10,000 hypothetical patients)	50-year Markov model	Markov model focusing on nephropathy	Markov model Monte Carlo simulation (10,000 iterations)
PERSPECTIVE	That of the English National Health Service (NHS)	That of a third-party payer in France	That of the insurer	That of the insurer
COHORT		Simulation of a cohort equivalent to the DCCT primary intervention cohort over 50 years	Cohort of 14-year-olds newly diagnosed with type 1 diabetes	
DATA SOURCE AND ASSUMPTIONS	The transition probabilities were obtained from the literature. The quality-adjusted life-years (QALY) calculation is based on data from a study involving adolescents that reported a 5.3% improvement in the quality-of-life index with the pump compared to multiple injections. The pump was assigned a utility of 1.0 (full health), and the utility of multiple injections was set at 0.947. A lower monthly utility value was assigned to reflect hypoglycemic and ketoacidotic episodes.	The probabilities of developing complications and HbA_{1c}-dependent adjustments were derived from published, peer-reviewed clinical trials and population studies, including the DCCT, the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), the UK Prospective Diabetes Study (UKPDS) and the Framingham Heart Study. Assumed a 1% gain in the HbA_{1c} level, a 50% reduction in the risk of severe hypoglycemic episodes with the pump, and a ketoacidosis event rate of 3.09% versus 1.39% between the pump and multiple injections, respectively.	The transition probabilities and the changes in probabilities associated with improved HbA_{1c} levels, and the costs of treatments and complications were derived from the scientific literature.	The efficacy and complication incidence data were taken from the scientific literature.
BENEFITS/ OUTCOMES CONSIDERED	Gain in QALYs due to the reduction in hypoglycemic and ketoacidotic episodes.	Reduction in the costs associated with renal dysfunction, foot ulcers, cardiovascular diseases and amputations Improvement in life expectancy	Reduction in renal complications and improvement in life expectancy	Gain in QALY due to the reduction in the number of cases of retinopathy and nephropathy and to the avoided deaths (due to severe hypoglycemia or to ketoacidosis)
COSTS	The data concerning the costs and interventions are from English databases (published scientific data).	The direct cost values for the treatment and complications are from the scientific literature.	The long-term costs and the incremental costs per life-year gained are derived from the model.	The costs are those in the Catalonian health-care system.

Economic studies (Cont'd)

AUTHORS	Scuffham and Carr, 2003	Roze et al., 2002 Abstract	Roze and Palmer, 2002 Abstract	De Sola-Morales et al., 2004 Conference paper (forthcoming AATRM publication)
RESULTS	Over an 8-year period, an average patient could expect to gain 0.48 QALYs (standard deviation [SD]: 0.20). The additional cost over 8 years for this gain was £5,462 (SD: £897). The incremental cost per QALY (Δcost/ΔQALY) was £11,461 (SD: £3,656). Pump therapy was more cost-effective in patients who had at least two severe hypoglycemic episodes per year and who required admission to hospital at least once every year. The results were sensitive to the number of hypoglycemic episodes and to the utility weights used to estimate QALYs.	1-year gain in life expectancy with the pump and an increase in total lifetime costs of €1,348 per patient. The cost of €1,348 per life-year gained is acceptable by the usual standards.	Life expectancy increased by 0.81 years with the pump, and the cost per life-year gained varied from US$38,807 and US$115,082, depending on whether the discount rate was 0 or 3%.	Gain of 17.14 QALYs with multiple injections and of 17.27 QALYs with the pump. This gain is associated with a mean cost of €64,368 and €100,265, respectively, for a an incremental cost per QALY of €288,117. These figures are quite far from the theoretical willingness-to-pay threshold of €30,000. The acceptability curve indicates that generalizing pump therapy would not be acceptable, even if the willingness-to-pay thresholds were much higher.
CONCLUSIONS	Pump therapy is a cost-effective investment when targetted at the patients who have at least two severe hypoglycemic episodes per year and who require at least one hospitalization. Other criteria should be considered, such as the patient's ability and motivation, and a low risk of treatment discontinuation.	The pump's benefits in terms of glycemic control and the reduction in the risk of hypoglycemic episodes seem to offset the disadvantages associated with increased program implementation costs and the treatment of ketoacidosis.	The improvement in the HbA_{1c} level observed with the pump may reduce renal complications and increase life expectancy. The additional costs are, to some extent, offset by the savings due to the decreased cost of treating renal failure. Further improvements in life expectancy and costs could be expected if other avoided complications are considered.	Pump therapy is more effective in the long term than multiple injections, but at a much higher cost. The high incremental costs per QALY suggest that the pump should be reserved for patients who are unsuccessful in achieving glycemic control with multiple injections.

Currency conversions (from January 1 to September 30, 2004): US$1 = CA$1.33; €1 = CA$1.63; £1 = CA$2.42 [Source: Bank of Canada]

APPENDIX G: COST DIFFERENTIALS FOR INSULIN PUMP THERAPY

TABLE G-1

Average-cost estimates for insulin pumps and accessories

	ANIMAS	DELTEC COZMO	MINIMED		AVERAGE COST*
			508	512/712	
Pump	$5,995	$5,800	$6,455	$6,000	
				Average cost of a pump	**$6,063**
Reservoir or cartridge	$388	NA	$201	$253	$281/year
Infusion set†	$1,900	NA	$2,136	$2,013	$2,016/year
Batteries	$112	$60	$116	$60	$87/year
				Average cost of accessories	**$2,384/year**

* The costs have been converted into 2004 Canadian dollars (€1 = CA$2.42; US$1 = CA$1.33; 2002-04 CPI (consumer price index) = 2% [Source: Bank of Canada currency converter; January 1, 2004 to September 30, 2004]

† The cost of the infusion set includes the tubing (which has to be changed every six days) and the cannula (which has to be changed every three days). The calculation for this item is based on an average of the unit costs (tubing and cannula) multiplied by 61 (in the case where a change is made every six days) or by 122 (in the case where a change is made every 3 days).

These data are from promotional materials and price lists from the main pump manufacturers in North America (Medtronics/MiniMed, Animas and Deltec Cozmo), from telephone interviews with a nurse specializing in diabetes education and insulin pump use, and from telephone conversations with pharmacists in the Montreal area.

NA : Data not available

TABLE G-2

Average-cost* estimates for pump therapy training† and follow-up

PHASE 1: CHOOSING THE PUMP, PUMP START, AND STABILIZATION			AVERAGE COST
Prescription from medical specialist (pump and insulin): fees $670/7 hr → $96/hr	± 1 hr	$96	$96
Meeting with nurse ($26/hr)	± 2 hrs	$52	$52
Meeting with dietitian ($24/hr)	± 2 hrs	$48	$48
Adults: two 6-hour sessions (nurse time)	12 hrs	$312	$416
Children: training for parents and children (nurse time)	20 hrs	$520	
PHASE 2: COST OF SUPPORT AND FOLLOW-UP			
The first 6 weeks involve about twenty 30-minute meetings with the care team: physician, nurse, dietitian → ($48 + $13 + $12) x 20			$1,460
Telephone calls to the representative			Included in the service
Telephone calls to the nurse (about twenty 30-minute calls) for follow-up and support			$260
Average total cost of training and follow-up			**$2,332**

* The costs have been converted into 2004 Canadian dollars (£1 = CA$2.42; US$1 = CA$1.33; 2002-04 CPI = 2% [Source: Bank of Canada currency converter, January 1, 2004 to September 30, 2004].

† These data on training are from a survey conducted among adults and parents of children on pump therapy (December 2003), MedScape (examples of education programs—Ontario and Australia), and telephone interviews with key health professionals (nurse specializing in diabetes education and insulin pump use). The hourly rates are from documents in the collective agreement for health professionals (*CSN, Convention collective - nomenclature des titres d'emploi, des libellés et des échelles de salaires des syndicats affiliés à la Confédération des syndicats nationaux (CSN); Fédération de santé et services sociaux – CSN (FSSS-CSN) and Fédération des professionnels – CSN (SP-CSN), 2000-2002)*, and consultations with individuals who work for the *Fédération des infirmières et infirmiers du Québec* (FIIQ) (telephone interviews, September 30, 2004). The Web sites of the *Conseil du trésor* and *Emploi Québec* (2004) were also consulted.

TABLE G-3

Estimates of mean cost differentials for pump therapy supplies compared to multiple injection therapy (per patient, in 2004 Canadian dollars)

	YEAR 1	SUBSEQUENT YEARS
Lancets (blood glucose monitor)*		
Pump	$347	$329
Multiple injections	$219	$219
Cost differential	**$128**	**$110**
Test strips (blood glucose monitor)†		
Pump	$2,310	$2,190
Multiple injections	$1,460	$1,460
Cost differential	**$850**	**$730**
Urine ketone test strips‡		
Pump	$62	$62
Multiple injections	$62	$62
Cost differential	**$0**	**$0**
Antiseptic swaps§		
Pump	$50	$50
Multiple injections	$599	$599
Cost differential	**($549)**	**($549)**
Transparent adhesive dressings‖		
Pump	$58	$58
Multiple injections	$0	$0
Cost differential	**$58**	**$58**

* A pump user has to prick him/herself 12 times a day for the first three weeks and six times a day thereafter, while a diabetic on multiple injection therapy pricks him/herself an average of four times a day. The mean annual cost is therefore calculated as follows: (21 days x 12 x $0.15) + (343 days x 6 x $0.15) = $347 compared to multiple injection therapy: 365 days x 4 x $0.15 = $219.

† The reasoning behind the test strip cost calculation applies to the calculation of the mean cost of blood glucose monitor test strips (unit cost = $1).

‡ Both treatment modalities require the use of ketone test strips at the rate of one strip per day. The cost varies only according to the type of test, i.e. urine (unit cost = $0.71) or blood (unit cost = $2.00). Calculation: 365 days x $0.17 = $62 (the urine test is the one used more often).

§ The cost of the antiseptic swabs is associated with changing the cannula in the case of the pump and with the injection sessions in the case of multiple injections. Calculation for the pump: 1 swab every 3 days x unit cost of $0.41 = 122 days x $0.41 = $50. For multiple injections: 1 swab 4 times/day → 4 x 365 days x $0.41 = $599.

‖ The cost of the transparent adhesive dressings is largely underestimated (unit cost = $0.48), considering that nearly 50% of diabetics on pump therapy develop hypersensitivity to the adhesive and use products like Tegaderm™, whose unit cost is $3.86 (total cost of $470 per year per patient). In general, these products are not presently covered in Québec. Dressings are changed every three days.

The sources of information are the same for pumps and accessories.

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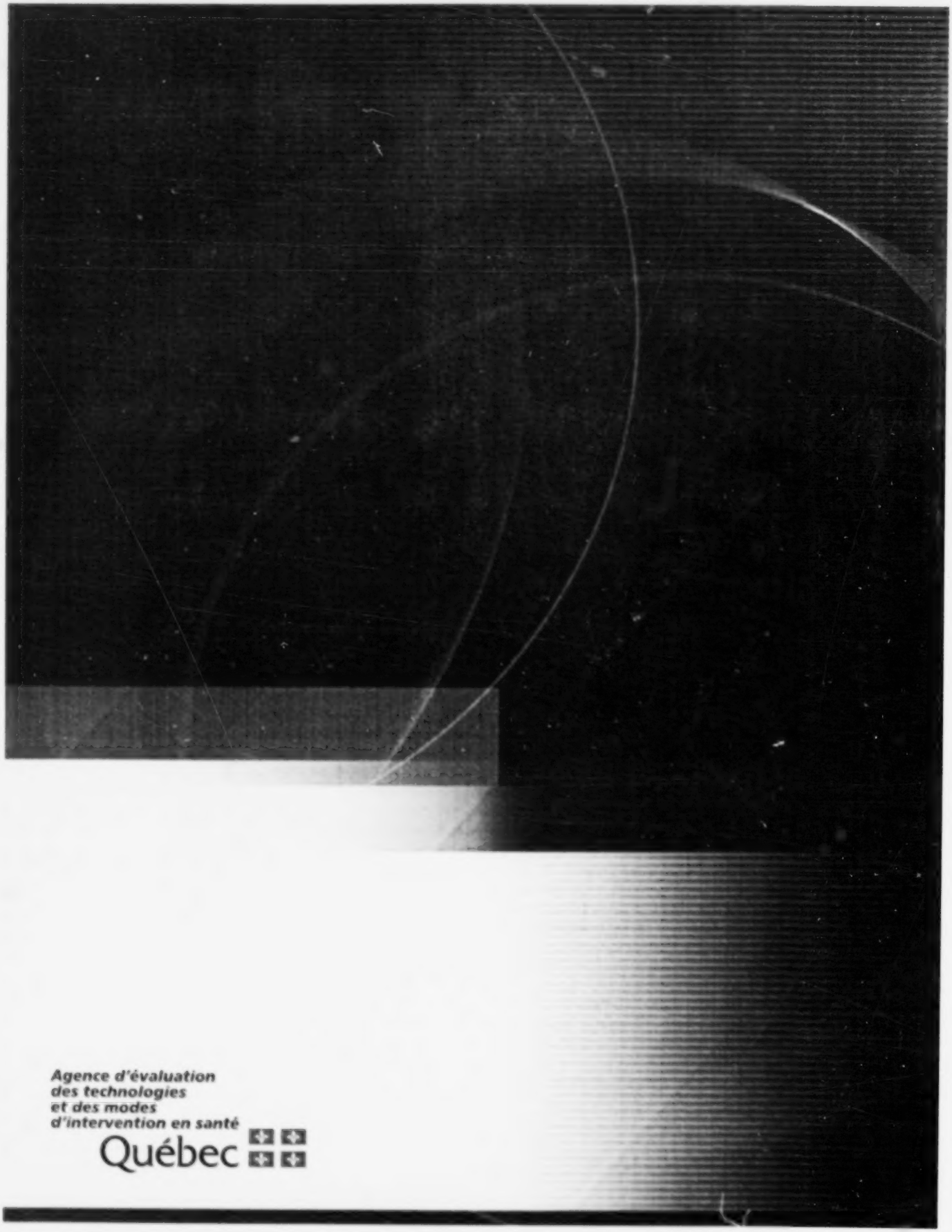

Agence d'évaluation des technologies et des modes d'intervention en santé

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